Enantioselective desymmetrisation using palladium catalysed coupling reactions

Claverie, Christelle Karine

Award date:
2001

Awarding institution:
University of Bath

UNIVERSITY OF BATH

Enantioselective desymmetrisation using palladium catalysed coupling reactions

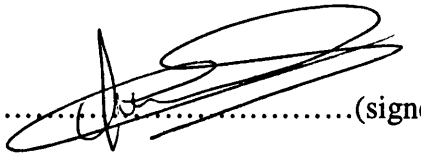
Submitted by Christelle Karine Claverie

For the Degree of PhD

Of the University of Bath

2001

COPYRIGHT



.....(signed)

06.12.2001.....(date)

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Abstract

The first chapter reviews the literature of enantioselective palladium catalysed reactions (Heck coupling, Grignard cross-coupling and Suzuki cross-coupling). The significant advancements in asymmetric catalysis and its application to natural product syntheses will also be discussed.

The second chapter reviews the literature related to enantioselective desymmetrisation, including the most relevant examples of enantioselective palladium catalysed desymmetrisation. Our strategy of desymmetrisation will also be presented including the design of selected *meso* substrates to be used in coupling reactions.

Chapter three reviews first, the preparation and uses of 1,1-dibromoalkenes in palladium catalysed reactions. The reactivity of selected 1,1-dibromoalkenes in various palladium coupling reactions will be described. The enantioselective desymmetrisation of these substrates *via* Suzuki cross-coupling reactions will also be discussed; this will include the main limitations of these type of substrates.

The fourth chapter first reviews the preparation and versatile use of triflates in palladium chemistry. The selective preparation of a range of cyclic mono and ditriflates will be presented. The results regarding the reactivity in Suzuki coupling reactions with achiral palladium catalysts will then be discussed. The enantioselective desymmetrisation of the prepared ditriflates will be presented.

Chapter five provides detailed experimental procedures.

Acknowledgements

Firstly, I would like to thank my supervisor Dr Mike Willis for his guidance and help throughout the past three years. My thanks go also to the students in my group; Selma the sunshine of the labs, Micky (Yeah,Yeah!), Steve la Fleur, Stav, Phil, Aaron, Marc and Vincent the little chef.

Members of the organic department past and present who I wish to mention for fun and help in and out of work include: Marc H., Parminder, Clarky, Moharem, Christian B., Phi, Lawrence, Gini, Matt P.L., Kerry J., Gian, Amin, Paul M., Christelle, Arimori, Tim (alias grand poulet/Titi), Catharine, Karine (allez, un petit pernod), Fred (so called l'Abbé Pierre), Koko the smiley face, JP (where is the cake?), Chris W., Jo the rugbyman, Laurence, Steve D., Piers, Suvi, Lara, Chris C. and any other people that I have forgotten to mention.
I would also like to thank Marie the dancing queen, as well as Maurizio, Rodolphe and Upul for their help and advice.

Many thanks go to my several proof-readers: Arimori, Selma, Micky, Mike E., Becky, Christelle, Matt P.L., Tim, Stav, Steeve la Fleur, and Phil B. Thank you very much for your work.

Many thanks to my past and present flatmates with whom I have had such good fun: Micky, Diego, J.P., Arach, Selma and Beth.

Many thanks to Dr Mary Mahon for the crystal structure analyses and to the technical support staff in the department, especially, Alan Carver and Ahmed. I would like also to thank the staff at the University of Swansea (Wales) for providing mass spectrometry analyses and Dr M. Wills for providing SEMI-ESPHOS ligand.

Enfin, merci Papa, Maman, Christophe, Martial et Francoise pour le soutien constant que vous m'avez apporte durant mes trois annees de these.

Abbreviations

abs. conf.	Absolute configuration
Ac	Acetate
AMPHOS	(-)-/2((*S*)-1-Dimethylaminoethyl)-phenyl-7-diphenyl phosphine
Ar	Aryl
9-BBN	9-Borabicyclo[3.3.1]nonane
BINAPFu	2,2'-Bis(diphenylphosphino-3,3'-binaphtho[2,1-b]furan
BINAPAs	2-Diphenylarsino-2'-diphenylphosphino-1,1'-binaphthyl
Bn	Benzyl
cat.	Catalytic (amount)
(*S*,*S*)-CHIRAPHOS	(2*S*,3*S*)-Bis(diphenylphosphino)butane
CI	Chemical ionisation
conc.	concentrated
conv.	Conversion
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]-7-undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DIOP	(-)-2,3-*o*-*Iso*propylidene-2,3-dihydroxy-1,4-bis (diphenyl phosphino)propane
DIPT	Di*iso*propyl tartrate
DMA	*N*,*N*-Dimethylacetamide
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNPH	1,4-Dinitrophenylhydrazine
dppb	1,4-Diphenylphosphinobutane
dppp	1,3-Diphosphinopropane
ee	Enantiomeric excess
EI	Electron impact
eq	Equivalent
Et	Ethyl

Et_2O	Diethyl ether
FAB	Fast atom bombardment
g	Gram
h	Hour(s)
HPLC	High pressure liquid chromatography
$(Ipc)_2BH$	Di*iso*propylcamphenylborane
*i*Pr	*iso*-propyl
IR	Infra red
(*R*,*S*)-JOSIPHOS	(*R*)-(-)-[(*S*)-2-(Diphenylphosphino)ferrocenyl]ethyl dicyclohexylphosphine
KHMDS	Potassium hexamethyldisilazide
L	Ligand
L*	Chiral ligand
LDA	Lithium d*iiso*propylamide
m	Multiplet
Me	Methyl
(*R*,*R*)-Me-DUPHOS	(-)-1,2-Bis((2*R*,5*R*)-2,5-dimethylphospholano)benzene
(*S*)-MeO-MOP	2-Diphenylphosphino-2'-methoxy-1,1'-binaphthyl
mg	Milligram
min	Minute(s)
mL	Millilitre(s)
Mp	Melting point
MS	Molecular sieves
n	normal
NAPHOS	2,2'-(*S*)-Bis(diphenylphosphinemethyl)-1,1'-binaphthyl
Nf	Nonafluorobutyl sulfonate
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
o	*ortho*
(*R*)-OH-MOP	(*R*)-2'-diphenylphosphino-1,1'-binaphthalen-2-ol
p	*para*
Ph	Phenyl
(*R*)-[2,2]-PHANEPHOS	4,12-Bis(diphenylphosphino)[2,2]paracyclophane C1-2
PHOX	Phosphinoxazoline
PMHS	polymethylhydroxysilane

PMP	Pentamethyl pyridine
PNBCl	*Para*-nitro benzyl chloride
(*S*,*R*)-PPFA	(*S*)-*N*,*N*-Dimethyl-1-[(*R*)-2-diphenylphosphino]ferrocenyl ethyl amine
PROPHOS	1,2-Bis(diphenylphosphino)propane
q	Quartet
p-TSA	*para*-Toluenesulfonic acid
py	Pyridine
(*R*)-QUINAP	(*R*)-(+)-1-(Diphenylphosphino-1-naphthyl)isoquinoline
rt	Room temperature
t	Triplet
TBDMS	*Tert*-butyldimethylsilyl
*t*Bu	*tert*-butyl
TEA	Triethylamine
Tf	Trifluoromethyl sulfonate
TFP	Tri-2-(furyl)phosphine
THF	Tetrahydrofuran
TIPS	Tri*iso*propylsilyl
TLC	Thin layer chromatography
TMGA	Tetramethyl guanidine
Tol	Tolyl
(*R*)-tol-BINAP	(*R*)-(+)-2,2'-Bis-(di-*p*-tolyl-phosphino)-1,1'-binaphthyl
t_r	Retention time

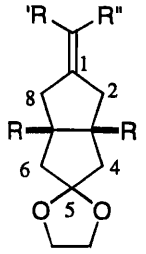
Contents

Stereochemical notation and compound numbering

Troughout this thesis, the graphical representation of stereochemistry used is in accord with the convention proposed by Maehr.[a] Thus, solid and broken wedges are used to signify absolute configuration, while the use of solid and broken lines refers to racemic materials. For the former, greater narrowing of both solid and broken wedges indicates increasing distance from the viewer.

Racemic Single enantiomer

Compound names conform as closely as possible to IUPAC nomenclature except for compounds possessing the *cis*-bicyclo[3.3.0]octane skeleton where the assignment of protons and carbons in the NMR data follows the numbering described below.



a) Maehr, H. *J. Chem. Ed.*, **1985**, 62, 114.

Chapter 1: Palladium catalysis

Introduction

Palladium is particularly useful and versatile amongst the many metals used in organic chemistry.[1] Palladium catalysts demonstrate an ability to catalyse a variety of C-C bond forming reactions, whilst being relatively stable to oxygen, moisture and a wide range of functionality. The use of chiral ligands in combination with palladium allows enantioselective catalysis. This is very important in the synthesis of pharmaceutical products, where the activity and toxicity of enantiomers may differ greatly.[2] The widespread use of palladium catalysed coupling reactions in synthesis is testament to new wide utility.[3]

During the last thirty years a large number of palladium catalysed reactions have been reported. The most studied reaction is arguably the Heck reaction which was discovered simultaneously in 1968 by a Japanese and an American group.[4,5] It is described as the reaction between an aryl or alkenyl halide or triflate and an alkene in the presence of a palladium (0) species and a base to generate a substituted (*E*)-alkene (Figure 1). The palladium catalysed coupling reactions of an aryl or vinyl halide or triflate can also be accomplished with organometallic compounds of lithium, magnesium, zinc, boron, aluminium and silicon in place of an alkene.[6] These reactions include the named reactions such as; the Grignard cross-coupling,[7,8] which employs organomagnesium reagents RMgX; the Stille coupling,[9,10] which utilises organostannane compounds $RSnR'_3$; and the Suzuki-Miyaura coupling[11-14] which involves the use of boron species $RB(OR')_2$ (Figure 1).

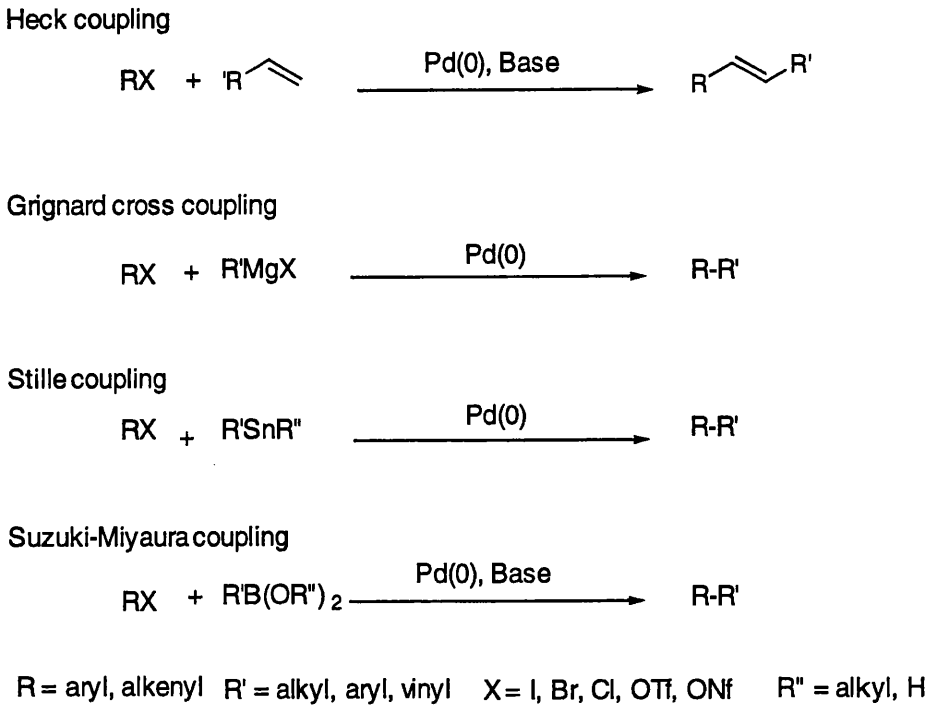


Figure 1

The mechanisms of these reactions have been extensively studied but are still not fully understood.[15,16] The first step is the oxidative addition of the aryl or alkenyl halide (or triflate) to the palladium (0) catalyst thus creating a σ-aryl or σ-alkenyl palladium (II) bond (Figures 2 and 3). The second step in the reaction is dependant on the substrate employed. Under Heck conditions, an alkene inserts into the palladium (II) species and an internal rotation follows (Figure 2). When an organometallic species (Grignard, Stille and Suzuki coupling) is used, a transmetallation from the metal to the palladium catalyst occurs (Figure 3). Evidence suggests that the transmetallation is the rate-determining step in most cross-coupling reactions.[14] Finally the catalytic cycle is completed with the reductive elimination which delivers the desired product and a hydropalladium species (Heck reaction) or regenerates the active palladium catalyst (in the cases of transmetallation). Heck coupling reactions thus, require the addition of a base to regenerate the active palladium species.

Mechanism of the Heck reaction

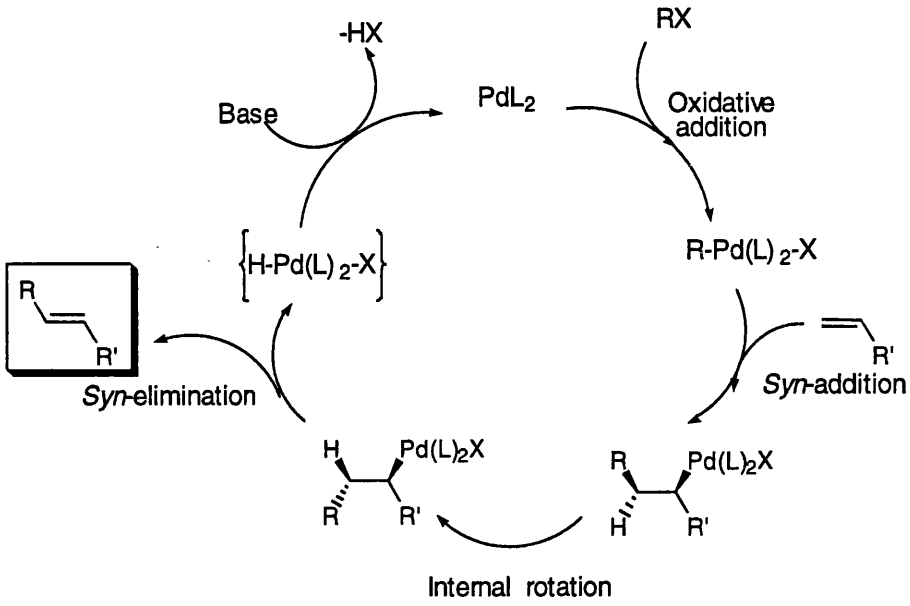


Figure 2

Mechanism of Grignard, Stille and Suzuki cross couplings

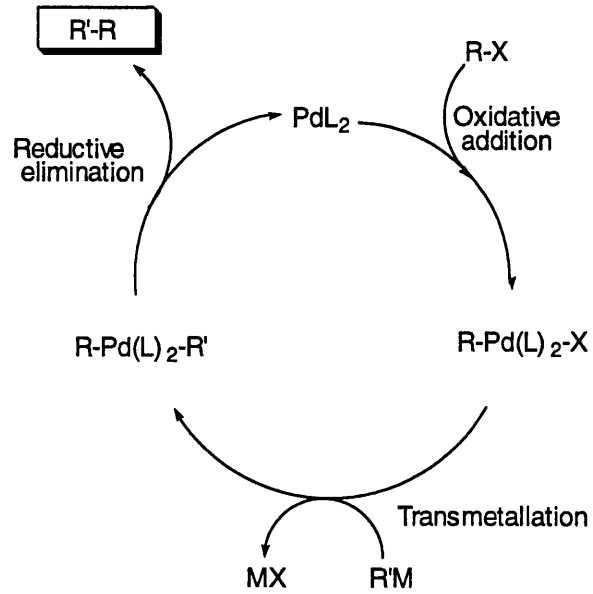


Figure 3

Enantioselective palladium catalysed reactions

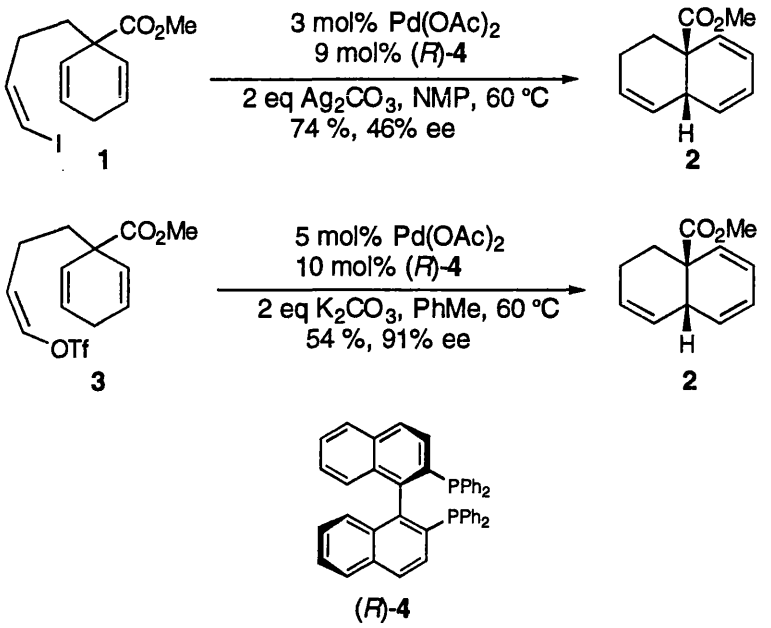
The growing need for the efficient synthesis of drugs and natural products containing chiral centres has led to the development of enantioselective palladium catalysed C-C bond forming reactions. The asymmetric induction is realised by the use of a chiral ligand which binds the palladium metal, allowing the transfer of the chiral information from the ligand to the prochiral substrate during the coupling reaction. Many chiral ligands have been synthesised and applied to palladium chemistry such as bidentate diphosphines, phosphinoxazolines and aminophosphine ligands.

In the following section several of the most impressive examples of asymmetric coupling reactions using palladium catalysts will be considered. This review will be limited to enantioselective Heck coupling, Grignard cross-coupling and Suzuki-Miyaura coupling reactions.

Enantioselective Heck coupling reactions

The Heck reaction can bring about unprecedented structural changes, especially when reactions take place intramolecularly. One of the first example of an asymmetric intramolecular Heck coupling reaction was reported by Shibasaki *et al*[17,18] who described the Heck reaction of the achiral vinyliodide **1** and vinyltriflate **3**. Both substrates produce the enantiomeric enriched decalin **2** when reacted with catalytic amounts of both $Pd(OAc)_2$ and ligand (*R*)-BINAP **4** (Scheme 1). The reaction performed with the vinyl iodide substrate gave the desired *cis*-decalin product in good yield (74%) but moderate enantioselectivity (46% ee). Conversely, the Heck coupling

utilising the vinyltriflate affords moderate yield (54%) and high enantioselectivity (91% ee).



Scheme 1

It was observed that the presence of a silver salt influenced the asymmetric induction when the iodide substrate was used. The salt causes the formation of a cationic palladium complex **6** in which the bidentate ligand remains fully chelated throughout the catalytic cycle (Figure 4). Triflate is a labile group, thus the Heck coupling proceeds without the silver salts required when using the iodide substrate.

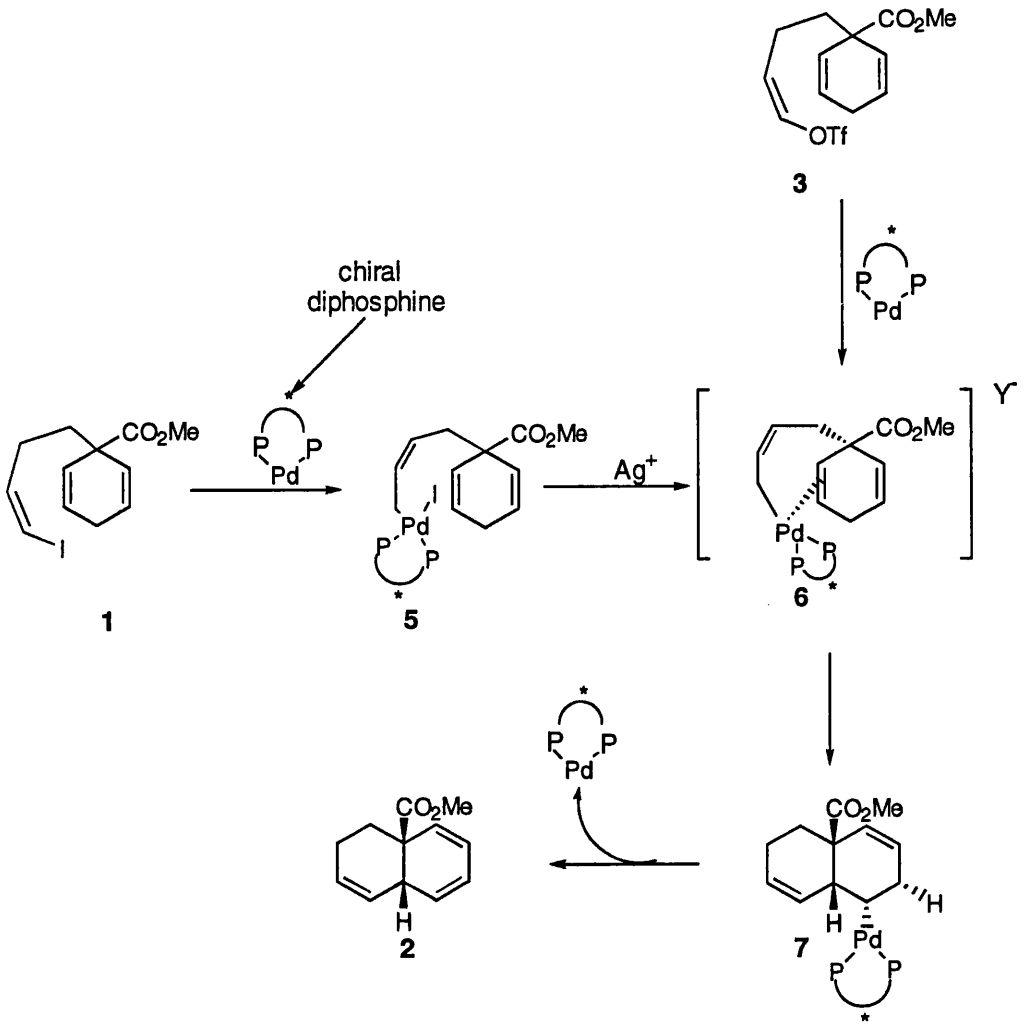
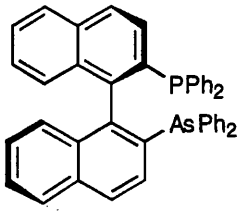


Figure 4

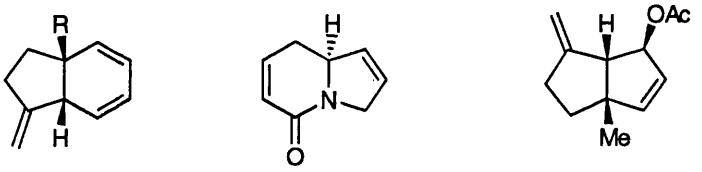
The modest ee reported for the conversion of **1** into **2** was improved as a result of a study of the effects on the reaction of varying the silver salt source. The best source of Ag^+ in respect of ee was found to be Ag_3PO_4 (due to the very low nucleophilicity of $Ag_2PO_4^-$), which gave the *cis*-decalin product **2** in 80% ee and 67% yield.[19] The newly reported ligand 2-diphenylarsino-2'-diphenylphosphino-1,1'-binaphthyl (BINAPAs) **8** (Figure 5) also increased the yield and ee for the Heck coupling of vinyl iodide **1** to the desired product **2**. After optimisation the product **2** could be isolated in 90% yield and 87% ee.[20]



8

Figure 5

This general method described for the synthesis of *cis*-decalin compounds has also been successfully applied to the synthesis of 6,5-ring systems through the formation of hydrindans **9**,[18] indolizidines **10**,[21] as well as the synthesis of 5,5-ring systems e.g. diquinanes **11** (Figure 6).[22]



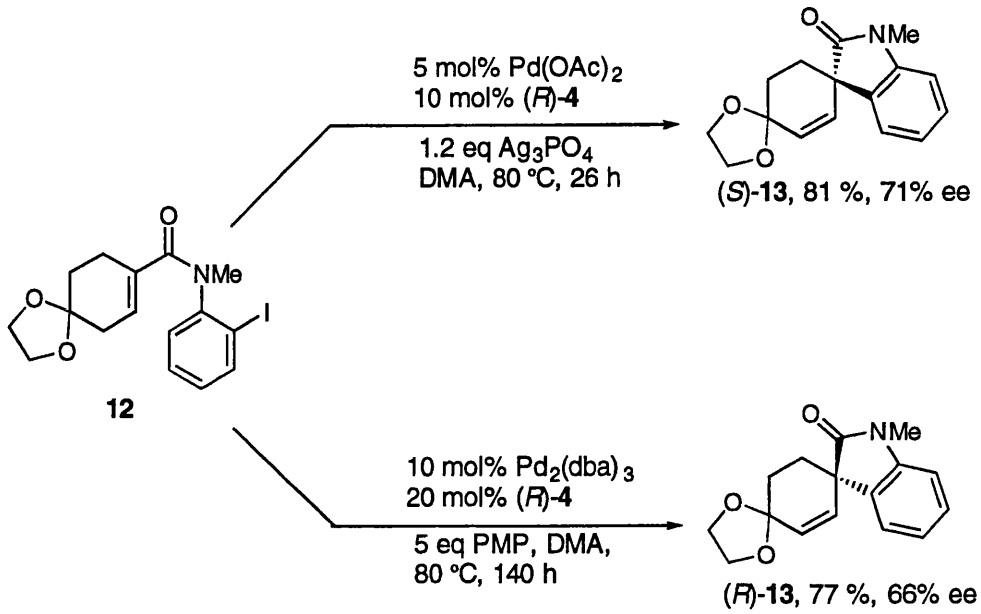
9 **10** **11**

R = CO_2Me, CH_2OTBS, CH_2OAc, CH_2OPv

Figure 6

These bicyclic compounds have been utilised as key intermediates in the syntheses of the natural products (-)-prepinnaterpene (hydrindan **9**),[23] lentiginosine (indolizidine **10**)[24,25] and $\Delta^{9(12)}$-capnellene-3β, 8β, 10α-triol (diquinane **11**).[26,27]

The enantioselective formation of quaternary carbon centres remains a significant challenge for chemists.[28,29] The first example using an asymmetric Heck reaction was reported by Overman *et al* in 1989.[30] However, the enantioselectivities obtained were moderate (45% ee) and the full potential of the approach did not become apparent until the publication of an interesting study related to the synthesis of spirooxindoles (Scheme 2).

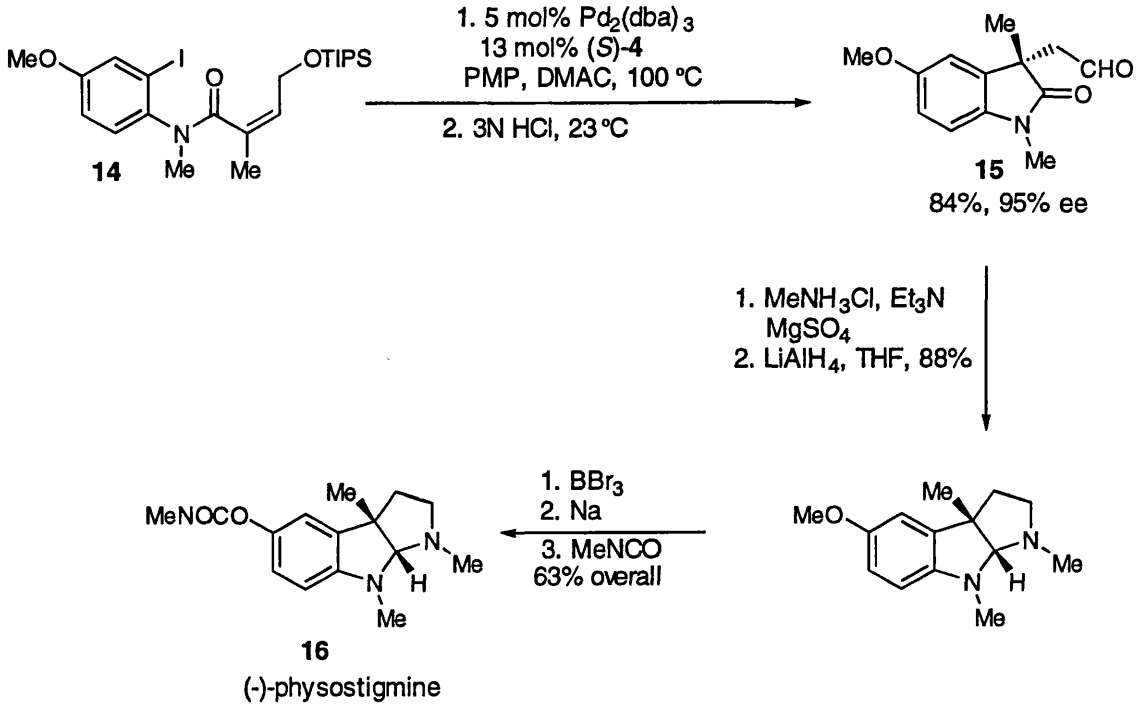


Scheme 2

The intramolecular Heck reaction of iodoanilide **12** with a catalytic amount of both palladium source and the ligand (*R*)-BINAP can remarkably lead to either enantiomer of desired product **13** by using two different kinds of HI scavenger.[31] Thus, the coupling of aryliodide **12** in the presence of a silver phosphate salt gives (*S*)-**13** in 81% yield and 71% ee. In contrast, when pentamethylpyridine is employed in place of the silver salt the opposite enantiomer (*R*)-**13** is formed in 77% and 66% ee. This interesting result requires a full mechanistic investigation into asymmetric Heck reactions since the cationic pathway does not seem to be the only mechanism that allows effective asymmetric induction.

The asymmetric Heck coupling reaction has been utilised in the synthesis of natural products. (-)-Physostigmine is a powerful inhibitor of acetylcholinesterase and is employed clinically to treat glaucoma and Alzheimer's disease.[32,33] Scheme 3 shows a synthetic sequence for this compound including an intramolecular asymmetric Heck coupling as a key step.

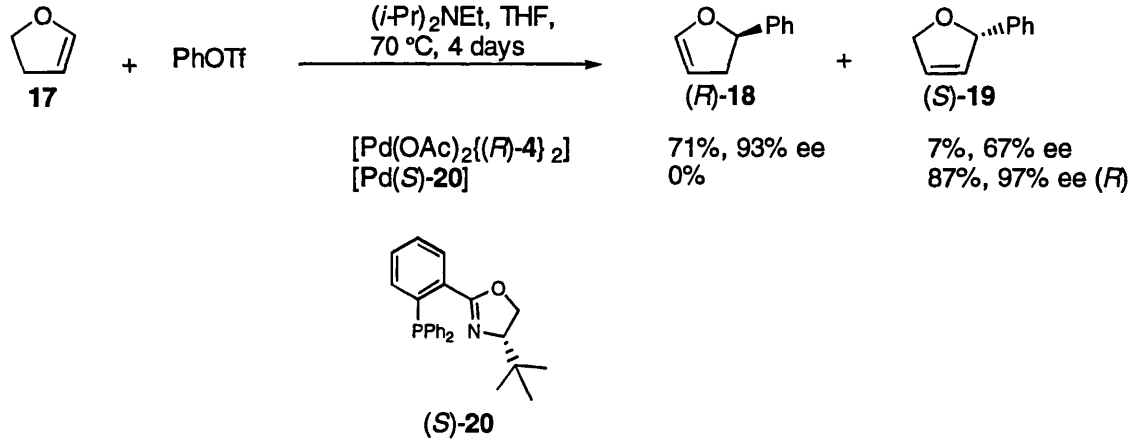
The hexadihydropyrrolo[2,3-b]indole **16** has been constructed by the intramolecular Heck reaction and hydroarylation.[34] The asymmetric cyclisation of enamide **14** using (*S*)-BINAP and $Pd_2(dba)_3$ in the presence of pentamethylpyridine affords predominantly (98:2) the (*E*)-enolsilane stereoisomer of the oxindole product, hydrolysis of which provides the (*S*)-oxindole aldehyde **15** in 84% yield and 95% ee.



Scheme 3

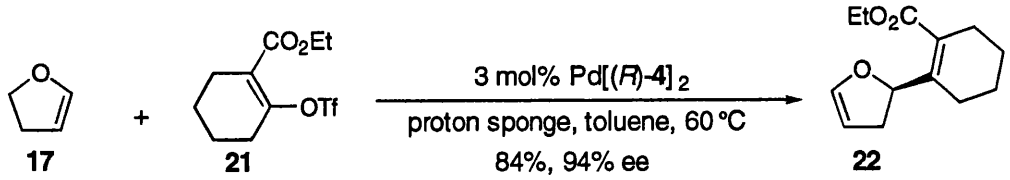
Asymmetric intermolecular Heck reactions have also been studied; the first example published in 1991 by Hayashi *et al* presented the asymmetric arylation of dihydrofuran **17** (Scheme 4).[35] The Heck coupling carried out in the presence of (*R*)-BINAP afforded (*R*)-2-phenyl-2,3-dihydrofuran **18** in 71% yield with up to 93% ee. Interestingly, the formation of regioisomer **19** (2-phenyl-2,5-dihydrofuran) in lower yield and moderate enantioselectivity was observed. The authors hypothesised that the catalyst can bind to either face of the substrate and the usual insertion and elimination steps follow.

However, in one case, unfavourable steric factors cause an immediate dissociation of the palladium species producing the minor product **19**. In the alternative diastereomeric palladium complex no steric interactions occur thus allowing the reinsertion of the alkene to the Pd-H bond followed by a second elimination to give the desired product **18**. The overall result is a kinetic resolution through a double bond isomerisation process. A promising result was reported by Pfaltz *et al*, using *t*-butylphosphinoxazoline **20** ((*S*)-*t*-Bu-PHOX).[36] In this case, no double bond isomerisation process can occur, which leads only to **19** with high ee (97%). Replacement of *t*-Bu group with a less bulky group in the oxazoline ligand **20** resulted in lower reaction rates while maintaining high enantioselectivivies.



Scheme 4

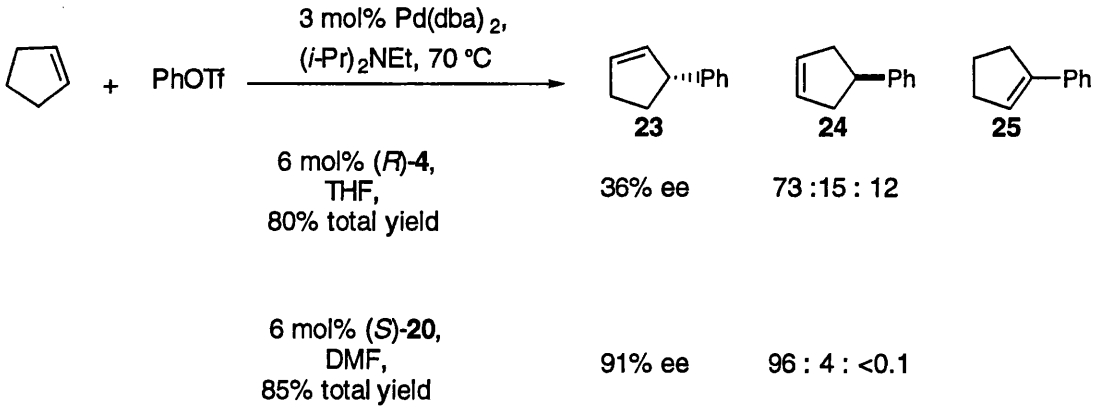
Impressive results have also been obtained using vinyl triflate coupling partners. For example the asymmetric Heck reaction between dihydrofuran **17** and triflate **21** with (*R*)-BINAP and a proton sponge in toluene gives the expected product **22** as the major product in 84% yield and 94% ee without any formation of the undesired regioisomer (Scheme 5).[37]



17 21 22

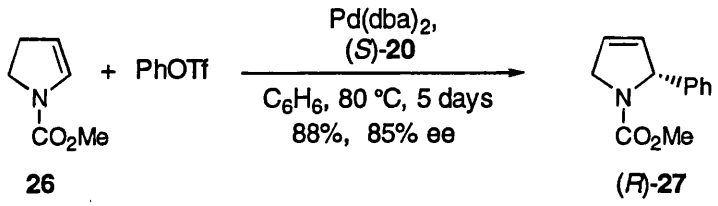
Scheme 5

The low tendency of the Pd(phosphinoxazoline) catalyst to promote C-C double bond isomerisation makes it possible to use substrates such as cyclopentene which are converted to mixtures of isomers with Pd(BINAP) catalysts (Scheme 6).[38] Thus the asymmetric Heck coupling of cyclopentene with phenyltriflate in the presence of $Pd(dba)_2$ and *t*-Bu-phosphinoxazoline (*S*)-**20** in DMF afforded 3-substituted cyclopentene **23** as a major product with excellent enantioselectivity (91% ee). Whereas the coupling carried out with (*R*)-BINAP **4** in THF leads to a mixture of expected product **23**, *meso* compound **24** and 1-phenylcyclopentene **25**. Moreover, in this case the chiral compound **23** was obtained with only moderate enantioselectivity (36% ee) due to double bond migration. The observed product distribution is dependent on the solvent and the base. The highest ee's as well as highest conversions and yields were observed in polar solvents such as DMF, DMF:H_2O (9:1) or THF.



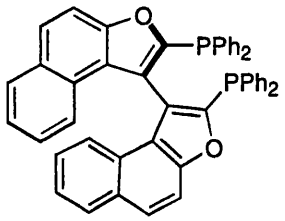
Scheme 6

The intermolecular asymmetric Heck reaction has also been applied to 2,3-dihydropyrrole derivatives.[38] The coupling usually requires prolonged heating at relatively high temperatures (Scheme 7). The coupling between 2,3-dihydropyrrole **26** and phenyltriflate in the presence of phosphinoxazoline ligand (*S*)-**20** produced exclusively the arylation product **27** with an ee of 85%. The corresponding 2,3-dihydro isomer was not detected whereas under similar conditions with a catalyst prepared from $Pd(OAc)_2$ and (*R*)-BINAP the 2,3-dihydro isomer was formed as a major product in 68% yield and 74% ee.

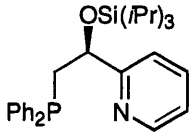


Scheme 7

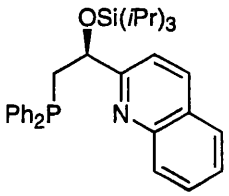
Asymmetric Heck reaction conditions have been well developed and optimisation studies have investigated the effect of bases, additives and solvents.[39] The majority of enantioselective reactions reported so far have utilised the BINAP ligand system which has usually proven to be very effective. The introduction of the *P,N* ligand phosphinoxazoline dramatically enhanced ee's of previously reported asymmetric Heck reactions. Further developments of the reaction are now focused on the design of different ligands which would lead to more efficient catalysts and thereby increase the rate of reaction. Recently a short five step synthesis of (+/-)-2,2'-bis (diphenylphosphino)-3,3'-binaphtho[2,1-b]furan (BINAPFu) **28** was reported (Figure 7).[40] The resolution of the racemic ligand was successfully achieved by use of (1*S*)-camphorsulfonyl azide. This ligand proves to give very good conversion and excellent enantioselectivity in the asymmetric Heck coupling of dihydrofuran and phenyl triflate.



28



29



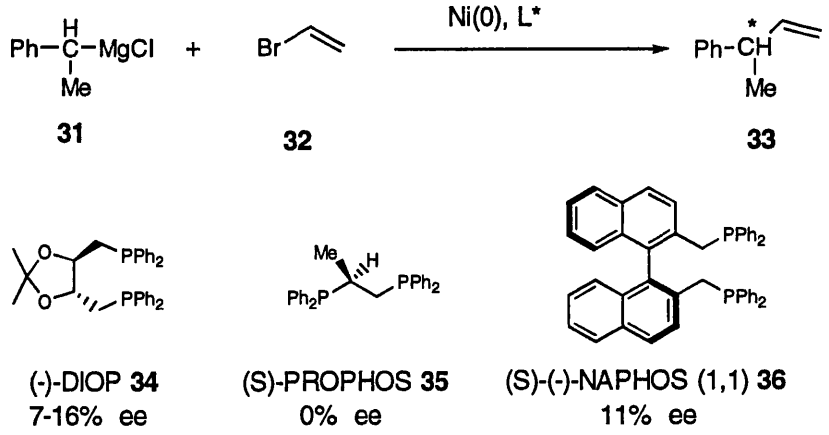
30

Figure 7

The synthesis of alternative *P,N*-ligands have also been achieved; Loiseleur *et al* synthesised new *P,N*-pyridine **29** and quinoline **30** type ligands.[41] The coordination geometry and the conformation of the diphenylphosphino groups in metal complexes of these ligands and the phosphinoxazoline ligand are very similar. The steric and electronic properties of the pyridine or quinoline ring on the other hand differ strongly from those of the oxazoline ring. These chiral ligands have been found to form efficient palladium catalysts for the asymmetric Heck coupling of 2,3-dihydrofuran and phenyl triflate. The bests results demonstrate conversions of up to 100% with 97% ee.

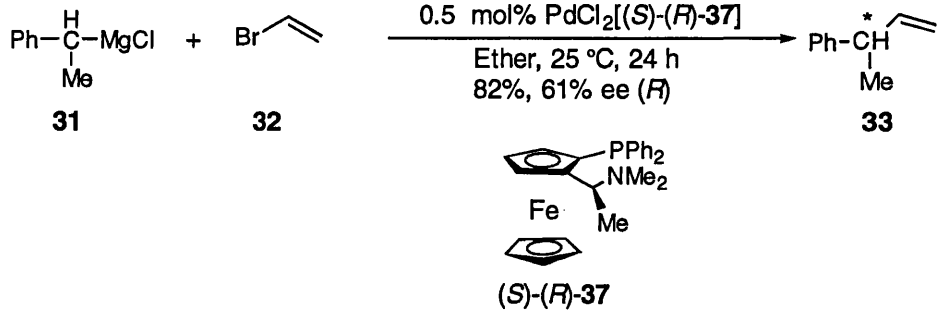
Enantioselective Grignard cross-coupling reactions

The first example of asymmetric Grignard reactions appeared in 1973 and involved the coupling between a secondary alkyl magnesium chloride **31** and vinyl halide **32** in the presence of nickel(0) and the ligand (-)-2,3-*o*-*iso*propylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane ((*R,R*)-DIOP) **34** (Scheme 8).[42,43] Unfortunately the enantiomeric purity of the vinylic product **33** was very low (7-16% ee). Two other chiral ligands (*S*)-1,2-bis(diphenylphosphino) propane (PROPHOS)[44] **35** and 2,2'-(*S*)-(-)-bis(diphenylphosphino methyl)-1,1'-binaphthyl (NAPHOS) **36** were employed in the Grignard cross-coupling but ee's remained very low (0-11% ee).[45]



Scheme 8

It was nearly ten years later that the first efficient asymmetric Grignard cross-coupling was reported by Hayashi *et al* who designed a series of ferrocenylphosphines easily prepared from Ugi's chiral *N,N*-dimethyl-1-ferrocenylethylamine.[46] (*S*)-*N,N*-Dimethyl-1-[(*R*)-2(diphenylphosphino)ferrocenyl] ethyl amine [(*S*)-(*R*)-PPFA] **37** was one the most effective ligands giving the coupling product 3-phenyl-1-butene **33** in up to 61% ee and 82% yield in the reaction of 1-phenylethyl magnesium chloride **31** (3 eq) with vinylbromide **32** (Scheme 9).[47] The use of substituted vinyl halide ((*E*)-β-bromostyrene and 2-bromopropene) resulted in a decrease of the enantioselectivity.



Scheme 9

The distinguishing feature of this type of ferrocenyl ligand is the combination of both planar and stereocentre elements of chirality as well as a functional group such as an amine on the side chain. The palladium catalyst, which is easily prepared by mixing dichlorobis(acetonitrile)palladium (II) and the phosphine (*S*)-(*R*)-PPFA in benzene,

shows chelation through the phosphorous and the nitrogen atoms by NMR (presence of two inequivalent methyl groups on the nitrogen). The authors carried out a study employing various ferrocenyl ligands with or without a chiral centre on the side chain and showed that the planar chirality in the phosphine ligands plays an important role and that the dimethyl amino group is the first requisite for the high stereoselectivity. The important role of the amino group may be rationalised by its strong ability to co-ordinate to the magnesium atom in the Grignard reagent as described in the mechanism shown in Figure 8.

When the Grignard reagent approaches the intermediate **38,** the dimethylamino group in the ferrocenylphosphine ligand dissociates from the palladium and coordinates to the magnesium atom in the Grignard reagent to form the transition state **39.** This coordination should occur selectively with one of the enantiomers of the racemic Grignard reagent and allow it to readily undergo subsequent transmetallation to form the organopalladium intermediate **40.** Reductive elimination to give optically active product **33** is followed by oxidative addition of the vinyl bromide to regenerate **38.**

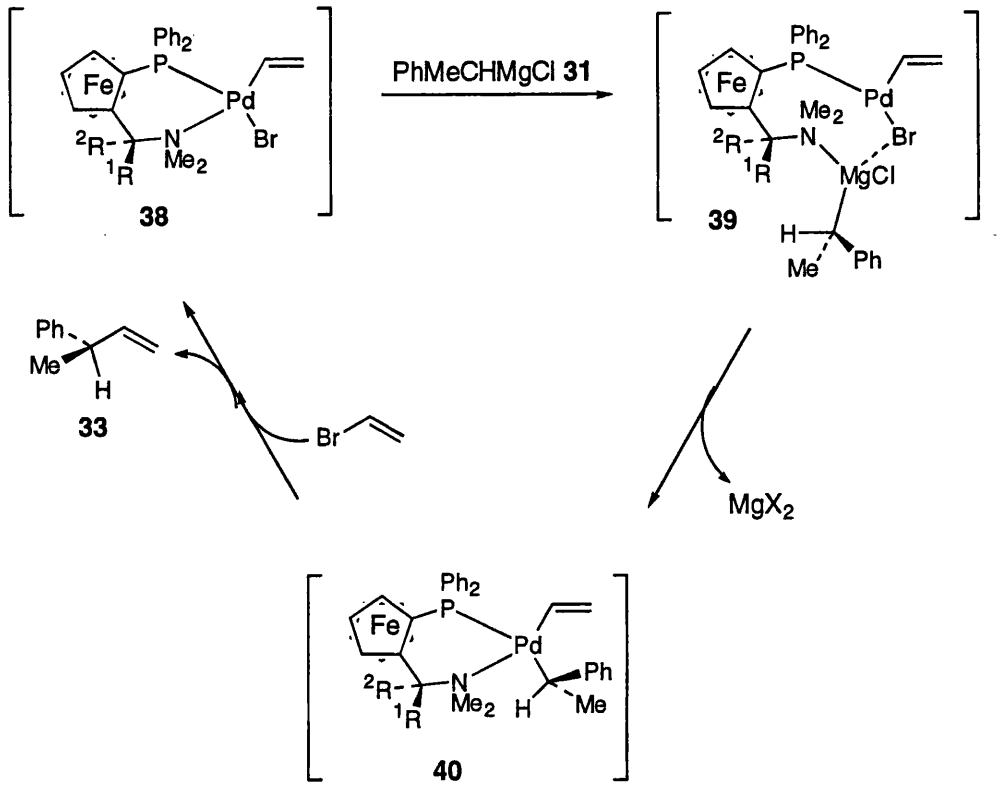
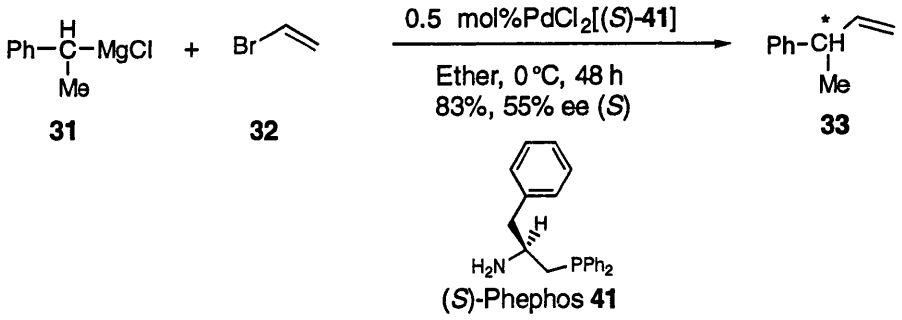


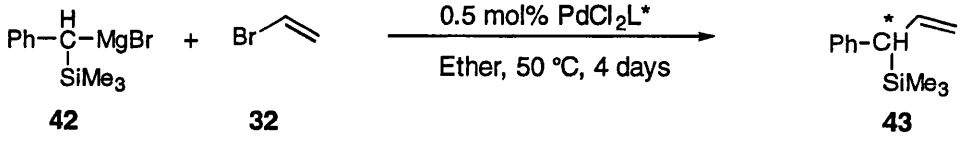
Figure 8

The same authors have synthesised a series of chiral (β-aminoalkyl)phosphines from readily available natural amino acids and they also observed that the presence of the dimethylamino group on the ligand is responsible for high enantioselectivity.[48] The use of the aminophosphines in the asymmetric Grignard cross-coupling of 1-phenylethyl magnesium chloride **31** with vinylbromide **32** did not enhance the enantioselectivity of the product **33** and the best result was achieved with the ligand (*S*)-Phephos **41** (which is the aminophosphine prepared from (*S*)-phenylalanine) affording the product in 83% yield and 55% ee (Scheme 10).

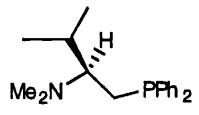


Scheme 10

The asymmetric Grignard cross-coupling has been applied to the synthesis of optically active allylsilanes which are useful intermediates in organic synthesis.[49,50] These allylsilanes contain an asymmetric carbon atom directly bonded to the silicon atom and are difficult to obtain by other methods. The coupling reactions between [α-(trimethylsilyl)benzyl]-magnesium bromide **42** and vinyl bromide **32** were performed with palladium catalysts from both ferrocenylphosphine ligands and aminophosphine ligands in ether at 50 °C (Scheme 11).[51,52] The silyl product **43** was formed in good yield (80%) and moderate enantioselectivity (56% ee) when $PdCl_2$[(*R*)-(*S*)-PPFA **37**] was employed whereas the use of $PdCl_2$[(*S*)-Valphos **44**] proved to be very active (98% yield) but delivered product **43** of much lower enantiomeric excess (7% ee).



	Yield	ee
$PdCl_2$[(*R*),(*S*)-**37**]	80%	56% (*R*)
$PdCl_2$[(*S*) -**44**]	98%	7% (*S*)

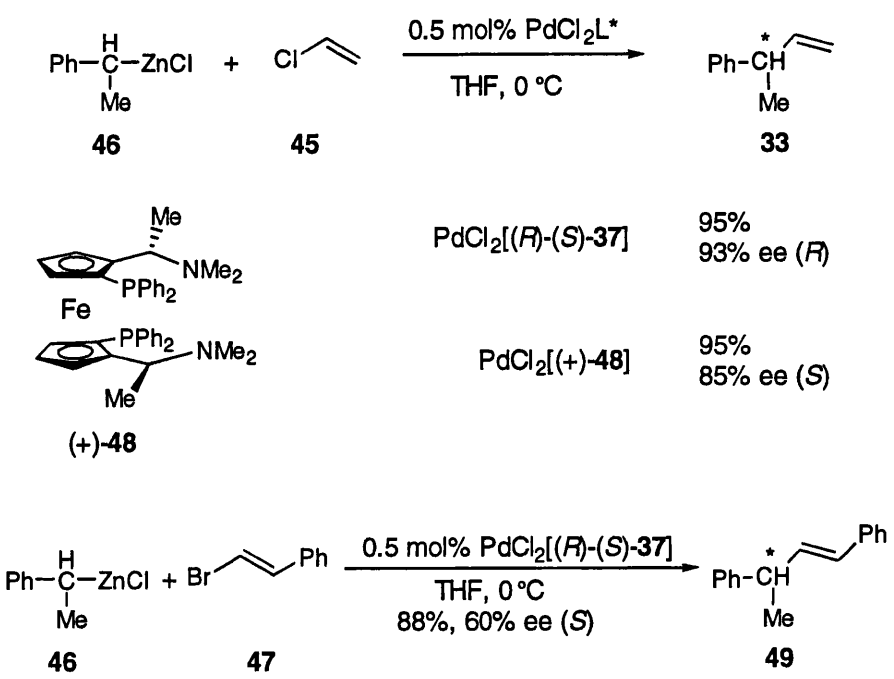


(*S*)-Valphos **44**

Scheme 11

It was shown that substituted vinyl bromide substrates such as (*E*)-bromostyrene and 2-bromopropene could successfully react with [α-(trimethylsilyl)benzyl]-magnesium bromide in asymmetric Grignard cross-couplings catalysed by $PdCl_2$[(*R*)-(*S*)-PPFA **37**] giving good yields of the expected products in 95% ee and 85% ee respectively. Unfortunately the same reaction carried out with phenylbromoacetylene did not afford the product in high enantiomeric excess (18% ee). The stereoselectivity of the Grignard coupling is strongly dependant on the substituents on the silicon atom and on the Grignard reagents. The best enantioselectivities were observed when the alkyl group is ethyl (93%).

The replacement of Grignard reagents with the corresponding zinc reagent has been shown in some cases to lead to higher enantioselectivity.[53] Thus vinyl chloride **45** and (*E*)-bromostyrene **47** are efficiently coupled with 1-phenylethyl zinc chloride **46** in the presence of different chiral palladium catalysts (Scheme 12). Among the ligands used is a new ferrocenyl diphosphine ligand (+)-**48** synthesised by Hayashi *et al* which was revealed to form an active palladium catalyst in the coupling of vinyl chloride **45** and 1-phenylethyl zinc chloride **46** yielding quantitatively the product **33** with good enantiomeric excess (85% ee).[54] The ligand of choice is still the ferrocenyl phosphine (*R*)-(*S*)-PPFA which allows the formation of the products **33** and **49** with the highest enantiomeric excess (respectively 93% and 60% ee).



Scheme 12

New chiral phosphines have been designed and utilised in enantioselective Grignard cross-coupling. For example Kreuzfeld *et al* prepared (-)-2((*S*)-1-dimethylaminoethyl)-phenyl-7-diphenylphosphine (AMPHOS) **50** (Figure 9) a similar ligand to ferrocenyl phosphine (*R*)-(*S*)-PPFA where the ferrocene sandwich is exchanged for a benzene ring.[55] The coupling of (*E*)-β-bromostyrene and 1-phenylethyl magnesium chloride in the presence of $PdCl_2$((*S*)-AMPHOS **50**) gave quantitative yield of the desired product with low enantioselectivity of 40% ee. However, when a tricarbonyl chromium unit is complexed to the phenyl ring, the stereoselectivity rises to 61% ee and is comparable to those observed for the coupling reaction of 1-phenylethyl magnesium chloride in the presence of the chiral ferrocenylphosphine ligands.[56] This further example shows the importance of the planar chirality in ligands employed in asymmetric Grignard cross-coupling reactions.

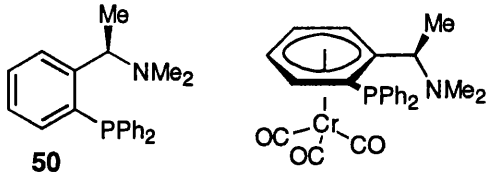
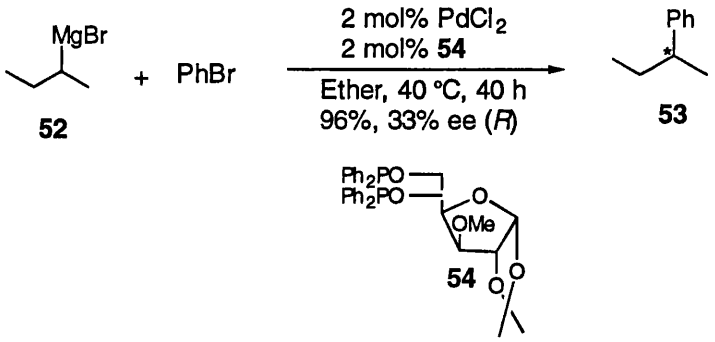


Figure 9

The cross-coupling of Grignard reagents lacking a phenyl substituent is usually difficult because of competitive isomerisation and elimination reactions. The first successful coupling of *s*-butylmagnesium bromide was reported in 1988 and was carried out with chiral diphenylphosphines and diphenylphosphinite derivatives of carbohydrates.[57-59] These ligands have a rigid structure and were readily prepared from the natural sugars *D*-galactose, *L*-rhamnose and *D*-glucose by known methods.[60] The highest selectivity (33% ee) was observed when the *D*-galactose derived ligand **54** was used in the asymmetric Grignard cross-coupling of racemic *s*-butylmagnesium bromide **52** with bromobenzene (Scheme 13).

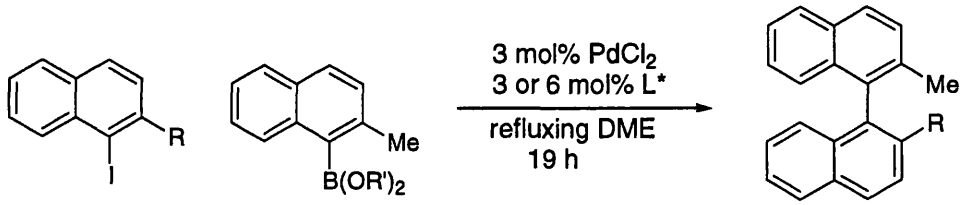


Scheme 13

Enantioselective Suzuki-Miyaura reactions

The coupling of organoboron substrates with aryl or alkyl halides or triflates catalysed by non chiral palladium catalysts has been widely studied and developed since the discovery of the reaction in 1978.[61,62] It was 24 years later that the first asymmetric Suzuki cross-coupling was reported independently by an English and an American group who described the enantioselective preparation of enantiomeric enriched naphthalenes which constitute an important class of atropoisomeric compounds.

Cammidge *et al* synthesised a series of axially chiral biaryl compounds by coupling naphthyl halides **55** or **56** and boronic acid or ester **57** or **58**.[63] The coupling reactions are successfully carried out in both homogeneous and heterogeneous conditions employing various bases ($Ba(OH)_2$, CsF, Na_2CO_3, NaOH) and solvents (DME/H_2O, DME, toluene/EtOH/H_2O). The ligand of choice is the aminophosphine ferrocenyl (*S*)-(*R*)-PPFA which gives the highest selectivity. With this ligand, 2-methyl-1,1'-binaphthalene **59** could be prepared in yields of 44-55% and ee's of 52-63%; the dimethyl derivative **60** gave the highest observed ee (85%) when boronic ester **58** was employed (Table 1).



55 R = H
56 R = CH_3

57 R' = H,H
58 R' = -CH_2CH_2-

59 R = H
60 R = CH_3

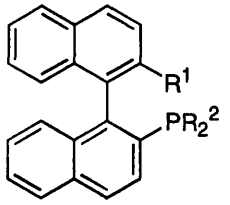
Table 1: Enantioselective Suzuki couplings of 1-iodonaphtalene derivatives

Entry	Halide	Boronate	Ligand[a]	Product	Base	ee %, (yield %)
1[b]	**55**	**57**	**37**	R(-)-**59**	$Ba(OH)_2$	63 (44)
2	**55**	**57**	**37**	R(-)-**59**	CsF	55 (44)
3	**55**	**57**	**37**	S(+)-**59**	CsF	21 (43)
4[c]	**56**	**58**	**4**	R(-)-**60**	CsF	85 (50)

[a] Reactions were carried out with 1.1-2.0 eq of boronic acid derivative using 3 mol% PdCl2 / 6 mol% monophosphine chiral ligand or 3 mol% PdCl2 /3 mol% bidentate chiral phopshine.
[b] Reaction was carried out in DME/H_2O. [c] Reaction was stopped after 6 days.

The use of a ferrocenyl monophosphine ligand where the dimethyl amine group is exchanged for a methoxy group showed the best reaction rate forming 74% of binaphthalene **59** after 19 h however the stereoselectivity was low (14% ee).

Buchwald *et al* also reported an asymmetric Suzuki coupling for the synthesis of axially chiral functionalised compounds employing various bulky electron rich phosphine ligands **61-66** and BINAP **4** (Figure 10).[64]



61 R^1 = Bu, R^2 = Cy
62 R^1 = $SiMe_3$, R^2 = Cy
63 R^1 = NMe_2, R^2 = Cy
64 R^1 = NMe_2, R^2 = *i*-Pr
65 R^1 = NMe_2, R^2 = Ph
66 R^1 = NMe_2, R^2 = *t*-Bu
4 R^1 = PPh_2, R^2 = Ph

Figure 10

The biaryl products were synthesised from either 2-dialkylphosphite-1-bromonaphthalenes **67** or **68** and (*ortho*)tolylboronic acids **69** or **70** or from 2-nitrohalobenzenes **73** or **74** and 2-phenyl-naphthylboronic acid **75** (Figure 11). The highest ee and yields were achieved when the monophosphine **63** was employed as the ligand. K_3PO_4 was found to be a more selective base than KF, CsF or KO*t*-Bu, and the use of 3 eq was shown to give the highest reaction rates and less catalyst loading was then required with reactions being complete within one day (when 2 eq of K_3PO_4 were used a reaction time of 96-140 h was necessary). Toluene was superior to THF as a solvent.

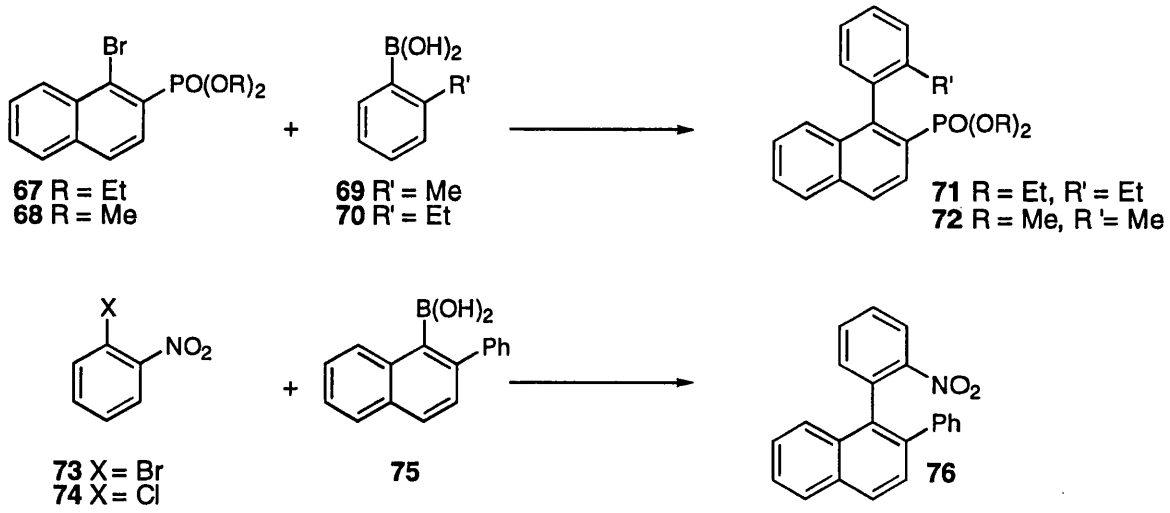


Figure 11

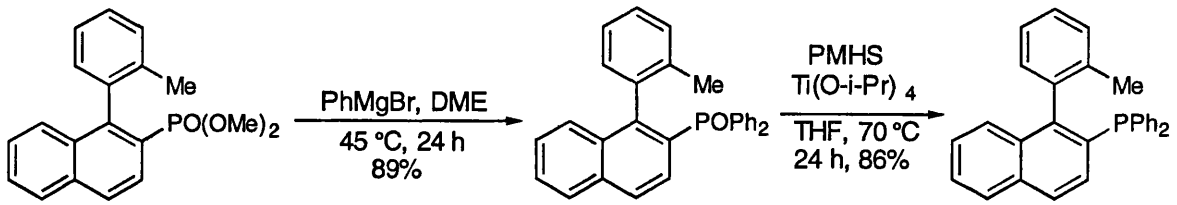
For example, the product **71** could be prepared in 96% yield and 92% ee by the Suzuki coupling between 1-bromonaphthalene **67** and phenylboronic acid **70** in the presence of 2 mol% of palladium (Table 2). Decreasing the catalyst loading to 1 mol% does not affect the yield or the enantiomeric excess of biaryl **71**. Even levels as low as 0.2 mol% could be employed to afford quantitative yields of substrate **72** in 86% ee.

Recrystallisation of the product **72** from DCM/hexanes gave 63% yield of the product in 99% ee.

Table 2: Enantioselective formation of biaryl compounds *via* Suzuki reactions

Entry	ArX	$ArB(OH)_2$	Product	mol % Pd	Time	Yield (%)	ee (%)
1	**67**	**70**	(+)-**71**	2	24	96	92
2	**67**	**70**	(+)-**71**	1	24	94	92
3	**68**	**69**	(+)-**72**	0.3	24	95	86
4	**68**	**69**	(+)-**72**	0.2	24	95	86
5	**73**	**75**	(+)-**76**	10	48	82	72
6	**74**	**75**	(+)-**76**	4	48	83	72

The phosphonates **71** and **72** have been further functionalised to optically pure monophosphines which could be employed as monodentate ligands in asymmetric reactions. For example, heating (+)-**72** (99% ee) with PhMgBr in DME at 45 °C for 24 h gave phosphine oxide **77** in 89% yield and with no loss in ee (Scheme 14). Reduction of **77** gave a new monophosphine ligand (-)-**78** in 86% yield and 99% ee.



(+)-**72** (99% ee) (-)-**77** (99% ee) (-)-**78** (99% ee)

Scheme 14

The reaction between allylic acetates and a nucleophile catalysed by palladium is known as allylic substitution. This coupling is also well studied and widely documented with many enantioselective examples being reported.[65,66]

Conclusions

Studies of enantioselective palladium catalysed reaction conditions have allowed access to coupling products in quantitative yields and high enantioselectivity. An important part of the development is devoted to the design of new efficient chiral ligands such as *t*-butylphosphinoxazoline employed in asymmetric Heck reactions, or ferrocenylphosphine derived ligands used in enantioselective Grignard cross-couplings. As a result of these powerful coupling reactions, various applications to the synthesis of natural products or drugs have been reported using an asymmetric Heck reaction as a key step.

A new approach towards the study of enantioselective catalysed palladium reactions will be introduced; the enantioselective desymmetrisation employing palladium coupling reactions. There have been several examples of such a strategy reported recently in the literature. In the next chapter a review of the concept of desymmetrisation followed by some literature examples related to palladium chemistry and finally the design of the selected substrates to be used for the cross-coupling reactions will be discussed.

Chapter 2: Enantioselective desymmetrisation

Introduction

When a plane of symmetry is present in a bifunctional *meso* molecule (containing stereocentres) the two halves are in most cases enantiotopic and can therefore be differentiated by reagents or catalysts capable of chiral recognition. The asymmetric desymmetrisation[67,68] process of an achiral or *meso* compound can thus be an alternative method for the synthesis of highly enantiomerically enriched products. The majority of the reported catalytic desymmetrisations involve the use of enzymes to differentiate between enantiotopic functional groups, however the number of non-enzyme catalysed systems is increasing.[69-71] This strategy has been used as a key step in the synthesis of a number of important target molecules.[72]

Desymmetrisation: principle

The enantioselective desymmetrisation of a bifunctional achiral or *meso* compound by use of a chiral reagent leads to the favoured formation of one of two enantiomeric products (Figure 12).

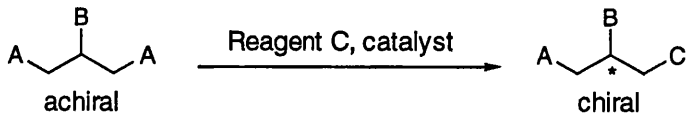


Figure 12

Furthermore, several examples have shown that the enantiomeric purity of the product of such reaction increases as the reaction proceeds due to *in situ* kinetic resolution of the products formed.[73,74] This attractive feature of enantioselective desymmetrisation has been well studied in asymmetric reactions of *meso*-diene substrates. The basic concept is illustrated in Figure 13 for a hypothetical epoxidation of a symmetric diene substrate.

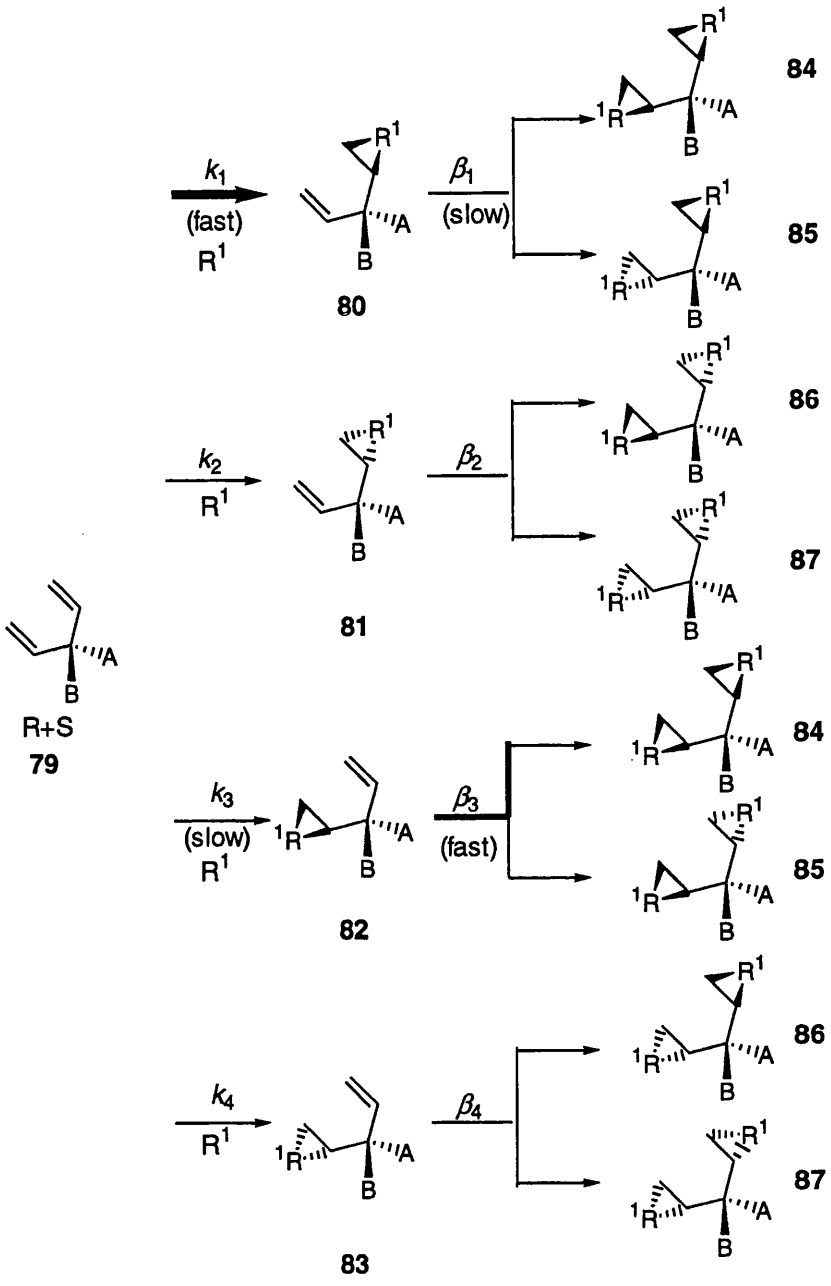


Figure 13

The attack of chiral reagent R^1 onto one of the double bonds of achiral diene **79** can lead to the formation of four stereoisomeric products **80**, **81**, **82** and **83** where **80** and **82** are enantiomers (and **81** and **83**). The reactions occur with a different rate k_i (i=1-4) for each of the four transformations. The formation of a major product, for example in asymmetric epoxidation, is the result of double stereoselection: an enantiotopic group differentiation is combined with a diastereotopic face differentiation (since A≠B in *meso*-diene **79**, the four faces of the substrate are different). The ratio **80/82** (thus the

ee) varies with time since destruction of the mono-epoxides occurs by the second addition of the remaining double bond. For example, if $k_1 > k_2$, k_3 and k_4 the major enantiomer **80** will have the "slow reacting" unsaturated group left whereas the minor enantiomer **82** will have the "fast reacting" unsaturated group available for a second addition reaction. The minor enantiomer **82** is expected to be selectively "destroyed" so that the ratio **80/82** should increase as the reaction proceeds. In order for the enhancement factor to operate effectively, large difference in the value of k_i's is required and the first addition should have little influence on the rate of the second addition. These issues will be suitably addressed if the chiral reagent has an intrinsic enantiotopic face differentiating capability and is highly sensitive to the stereodirecting properties of the allylic substituents A and B (for example preference for addition *syn* to the B group in the rotamer **79**).

On this bases, a mathematical model was developed by Shreiber *et al* which assumed that each reaction is first order in substrate and reagent.[75] The equation found shows that the ratio of enantiomers can become as large as desired just by achieving a conversion that is high enough.

A variety of reactions have been employed to illustrate this process.[76] An early example comes from the study of Partridge and Uskokvic on the asymmetric hydroboration of achiral 5-alkyl-1,3-cyclopentadienes.[77] The Sharpless asymmetric epoxidation reaction also serves to illustrate this process delivering mono-epoxide products which have proved to be synthetically useful intermediates.[78,79] The features of this reaction which are particularly attractive include facial discrimination by the reagent (reagent control) and the sensitivity of the reagent to substrate structure (substrate control).

For example, the asymmetric desymmetrisation of the *E,E*-divinylcarbinol **88** in the presence of catalytic amount of titanium tetra*iso*propoxide and *t*-butylhydroperoxide leads to either enantiomer **89** or **90** by appropriate choice of the Sharpless reagent ((-) or (+)-di*iso*propyl tartrate) (Table 3).[80]

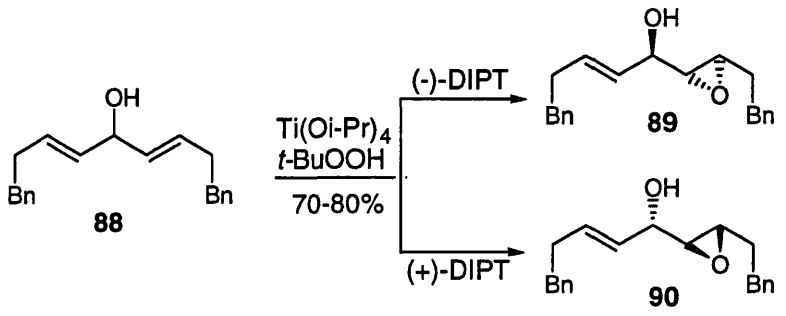


Table 3: Asymmetric epoxidation of **88**

	L-(+)-DIPT	
conditions[a]	% ee	% de
1 h, -25 °C	93	>97
3 h, -25 °C	95	>97
44 h, -25 °C	>97	>97

[a] 2.60 eq t-BuOOH, 1.15 eq Ti(O-*i*-Pr)$_4$, 1.50 eq L-(+)-DIPT with powdered 4ÅMS in DCM.

A study using natural L-(+)-di*iso*propyl tartrate was carried out: The results shown in Table 3 clearly indicate that the ee improves as the reaction proceeds toward to completion. The chiral mono-epoxide **90** was advanced through several steps to complete an enantioselective synthesis of KDO (2-deoxy-*D-manno*-2-octulonosicacid).[80]

The desymmetrisation of a *meso* molecule to yield enantiomerically enriched products is proving to be a powerful synthetic tool: The method has been employed to desymmetrise anhydride, alkene, diene and diol substrates by formation of C-O, C-N, C-S and C-Cl bonds using a wide range of transformations. The process can be

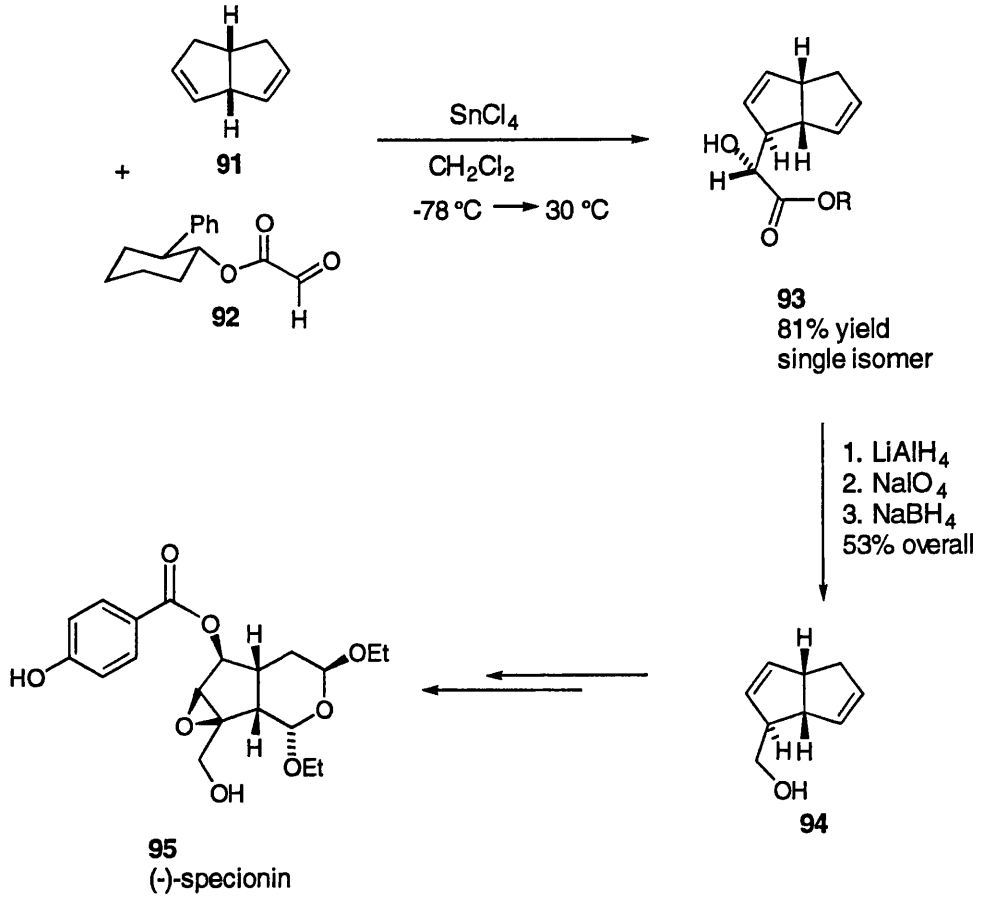
successfully carried out with stoichiometric or catalytic amounts of reagents (or catalysts).[76]

However the application of this strategy to the catalytic formation of C-C bonds has been less studied and only few examples have been reported so far.

Desymmetrisation by formation of C-C bonds

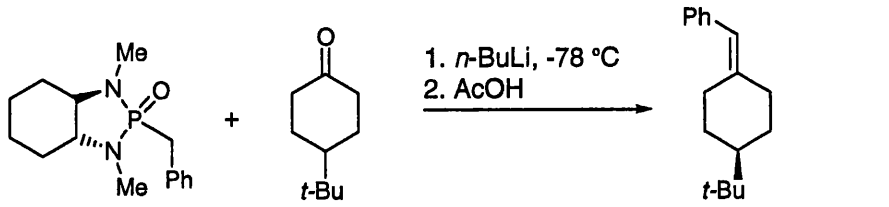
Non metal catalysed reactions

An early example of an enantioselective desymmetrisation involving the formation of C-C bond was reported by Whitesell.[81] He pioneered the use of chiral glyoxalate esters as enophiles in the intramolecular ene reaction. Reaction of cyclic *meso*-diene **91** with the glyoxolate ester **92** derived from *trans*-2-phenylcyclohexanol in the presence of tin tetrachloride in methylene chloride at -78 °C afforded the ene product **93** in 81% yield as a single isomer (Scheme 15). Reductive removal of the chiral auxiliary followed by oxidative cleavage provided allylic alcohol **94**. An eight step sequence starting from the chiral alcohol **94** was used to prepare (-)-specionin **95** in optically pure form.



Scheme 15

A further example of enantioselective desymmetrisation by C-C bond formation is related to the Horner-Wadsworth-Emmons reaction and involved the preparation and use of chiral phosphonates and phosphonamides. Hanessian has employed the phosphonamide **96** derived from *trans*-cyclohexane-1,2-diamine to desymmetrise a range of achiral ketones (Scheme 16). For example, treatment of phosphonamide **96** with *n*-butyllithium at -78 °C then reaction with 4-*t*-butylcyclohexanone **97** followed by acid treatment provides *exo*-alkene **98** in 91% yield and 98% ee.[82,83] The allyl substituted phosphonamide (in place of benzyl group) was also successfully employed affording stereochemically pure allylidene alkylcyclohexane products.

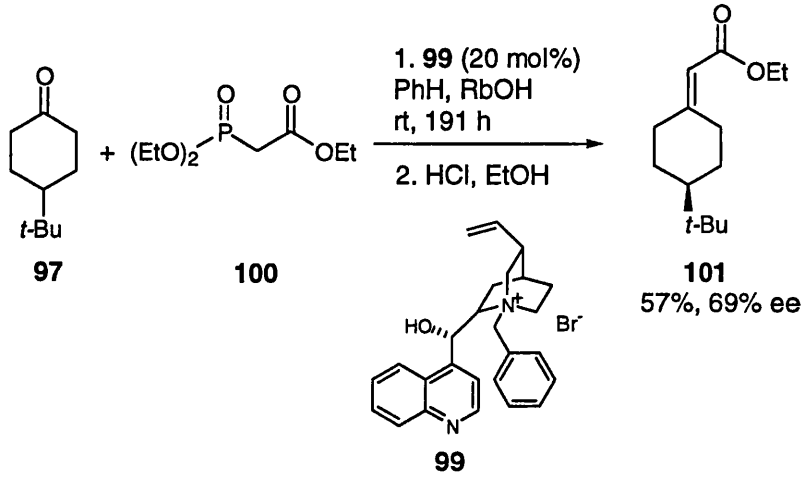


96 **97** **98**

>99:1er, 91%yield

Scheme 16

A catalytic asymmetric Horner-Wadsworth-Emmons reaction conducted under phase transfer conditions was reported recently.[84] Quaternary ammonium salt **99** derived from cinchonine, in combination with phosphonate **100** and rubidium oxide was found to effectively desymmetrise 4-*t*-butylcyclohexanone **97** (Scheme 17). These optimal conditions (employing 20 mol% of ammonium salt **99**) gave the product α,β-unsaturated **101** in 57% yield and 69% ee (Scheme 17). A range of counterions and different alkyl substituted catalysts were investigated, however all were found to be inferior to **99**.



97 **100** **101**

57%, 69% ee

99

Scheme 17

Enantioselective palladium catalysed reactions

Of all the transition metals used in catalysed C-C bond forming coupling reactions, palladium is the metal most employed. The palladium catalysed desymmetrisation of a *meso* compound containing two equivalent halogen or triflate groups likely to undergo the coupling reaction will be successful if enantiotopic discrimination is achieved. This selectivity will occur in the oxidative addition of the catalyst to one of the two carbon halogen or triflate bonds, thus generating a new chiral palladium species incorporating the substrate. Further functionalisation, for example by a Grignard cross-coupling of such a species will lead to the formation of an enantiomerically enriched product and provide a new method which would allow access to architecturally complex molecules in enantiomerically enriched form.

The use of this innovative strategy is however not well known and the first example of asymmetric desymmetrisation incorporating a palladium catalysed coupling was reported a few years ago. The next section will highlight the benefits of palladium catalysed desymmetrisation reactions and will be divided according to the type of palladium coupling employed.

Heck reactions

The first example of enantioselective desymmetrisation involving a Heck type reaction was reported in 1999 by Stephen Bräse.[85] The symmetric 1,3-bis(enolnonaflate) moiety **102** prepared efficiently in four steps from dimedone was treated under Heck conditions (5 mol% $Pd(OAc)_2$, 15 mol% chiral ligand, triethylamine, DMF) in the presence of *t*-butyl acrylate at 80 °C to provide highly congested hydrocarbon products (containing a quaternary carbon centre) in moderate to good yields and moderate ee's (Table 4). The

chiral *P,N* ligand *i*-Pr-phosphinoxazoline **104** was found to give the highest enantioselectivity (52% ee) whereas the use of diphosphine BINAP **4** afforded the bicyclo[4.2.0]octadiene product **103** in 57% yield and 27% ee.

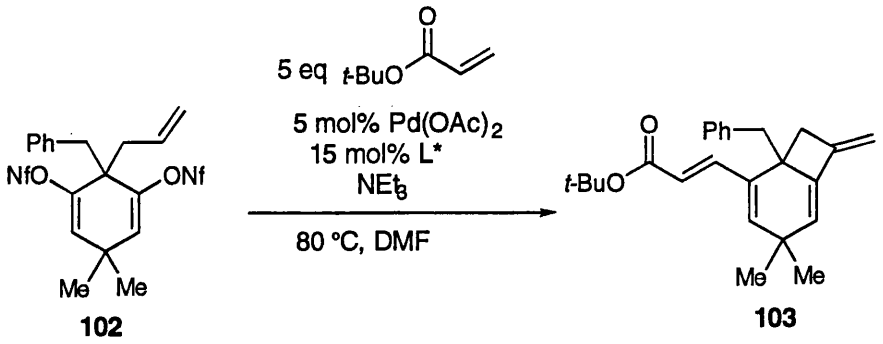
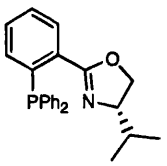
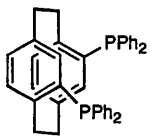


Table 4: Enantioselective desymmetrisation of bis-nonaflate **102**

Entry	L*	yield **of** **103** (%)	ee of **103** (%)
1	*R*-**4**	57	27
2	(-)-**34**	42	18
3	(*S*)-**104**	25	52
4	**105**	23	37



(*S*)-*i*-Pr-PHOX **104**



(*R*)-[2,2]-PHANEPHOS **105**

This reaction displayed some remarkable features: An *exo-trig*-cyclisation involving a Heck reaction has scarcely been observed[86,87] with this kind of 1,5-hexadiene substrate where palladium catalysed Cope rearrangement[88] is favoured to deliver differently substituted dienes which might resist cyclisation. However in the case of the ring annelated **102**, a Cope rearrangement to give **106** is not favoured since the chair type transition state **107** is energetically unfavourable for a Cope rearrangement (Figure 14).

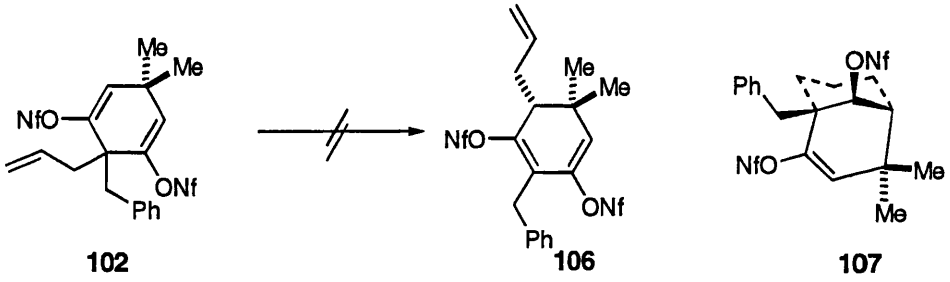
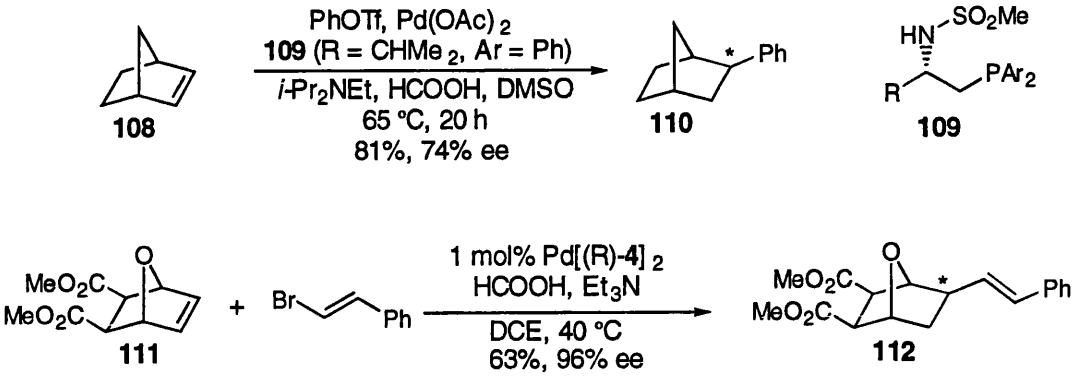


Figure 14

The combination of the Heck type hydroarylation/hydrovinylation of olefins with palladium catalysed cross-coupling reactions is an example of a three-component coupling reaction (alkene, aryl halide or triflate and formic acid as the hydrogen source). This coupling is not strictly a Heck reaction as the β-hydride elimination step is replaced by reductive elimination. It nevertheless shares a common pathway with regard to the enantioselective step.

The enantioselective desymmetrisation of norbornene employing a hydrophenylation reaction was first reported by Brunner *et al* in 1991 although the ee's obtained were low (<40%).[89] The system was revised and improved by use of novel phosphine ligands of the general structure **109**. When employing these chiral phosphine sulphonamide ligands in the asymmetric hydroarylation reaction the conversion of norbornene **108** to **110** could be carried out in 81% yield and 74% ee (Scheme 18).

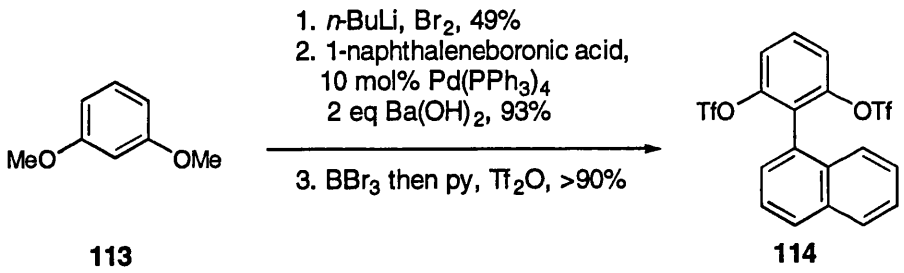
The use of Pd[(*R*)-BINAP]$_2$ was also found to effectively catalyse the asymmetric reductive Heck reaction using vinyl iodides and triflates on norbornene and on hetero-analogues such as **111**; excellent ee's and satisfactory yields were obtained (Scheme 18).[90] This reaction was further developed and applied to the synthesis of *N*-protected epibatidine with good enantioselectivity (81% ee).[91]



Scheme 18

Grignard cross-coupling reactions

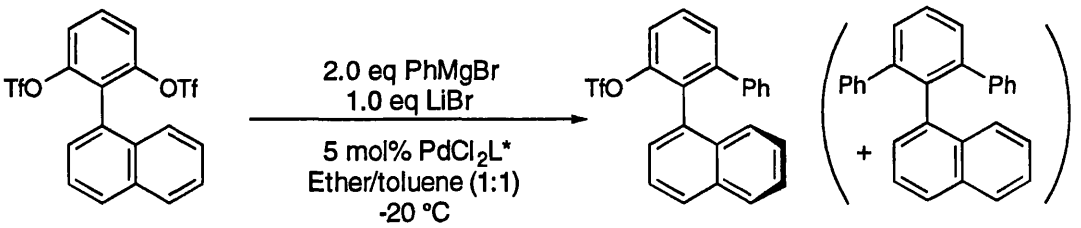
Axially chiral biaryls represented by 1,1'-binapthyls have found extensive use in a variety of asymmetric reactions. In most of the cases reported, the axial chirality of biaryls has been generated by the coupling of two biaryl units.[92,93] Hayashi *et al* have reported the first preparation of axially chiral biaryls which is realised by enantioposition selective substitution reaction of one of the two enantiotopic triflate groups on achiral biaryl triflates employing an asymmetric Grignard cross-coupling.[94] The achiral biaryl ditriflates were readily prepared from 1,3-dimethoxybenzene **113** which was subject to lithiation followed by bromination. The bromobenzene substrate was coupled with 1-naphthylboronic acid in the presence of barium hydroxide and 10 mol% of $Pd(PPh_3)_4$. Demethylation of methyl ethers with boron tribromide followed by triflate formation of the resulting phenols with trifluoromethanesulfonic anhydride gave ditriflate **114** in 41% overall yield (Scheme 19).



113 **114**

Scheme 19

The enantioselective Grignard cross-coupling of *meso*-ditriflate **114** in the presence of phenylmagnesium bromide, lithium bromide and chiral palladium complexes (generated from chiral aminophosphine, monophosphine and diphosphine ligands) enables the preparation of monosubstituted biaryl compound in remarkably good yields and excellent enantioselectivities (Table 5). The chiral aminophosphine ligands derived from natural aminoacids ((*S*)-alaphos and (*S*)-phephos) generate very efficient palladium catalysts: The best enantioselectivities (up to 90% ee) and best yields (up to 87%) were observed with these *P,N* ligands. However, the use of *i*-Pr-phoshinoxazoline, another *P,N* ligand, in the Grignard cross-coupling did not efficiently desymmetrise the achiral ditriflate **114**, delivering the product **115** in 26% yield and 52% ee. The reaction was very slow with palladium coordinated with the chelating bisphosphine ligand BINAP (2% yield). A palladium catalyst of axially chiral monophosphine ligand (*R*)-MeO-MOP[95] gave a low yield of **115** in 40% ee.

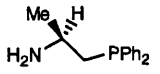


114 **115** **116**

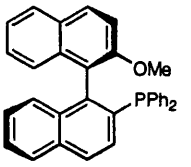
Table 5: Enantioselective desymmetrisation of ditriflate **114**

Entry	catalyst	yield of **115** (%)	yield of **116** (%)	ee % of **115** (abs. conf.) [a]
1	$PdCl_2$[(*S*)-**117**]	84	10	90 (*S*)
2	$PdCl_2$[(*S*)-**41**]	87	12	86 (*S*)
3	$PdCl_2$[(*S*)-**104**]	26	11	52 (*S*)
4	$PdCl_2$[(*S*)-**4**]	2	0	0
5	$PdCl_2$[(*R*)-**118**]$_2$	7	0	40 (*R*)

[a] Determined by HPLC analysis of phenol obtained by alkaline hydrolysis of triflate **114**.



(*S*)-alaphos **117**



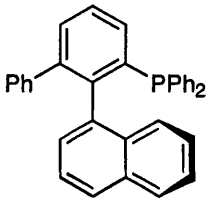
(*R*)-MeO-MOP **118**

The asymmetric desymmetrisation of *meso* ditriflate **114** was also successful when 3-methylphenylmagnesium bromide and triphenylsilylethynylmagnesium bromide were employed.[96]

It was found in the asymmetric cross-coupling of ditriflate **114** with PhMgBr that the enantiomeric purity of **115** was dependent on the yield of the diphenyl product **116**; such an observation is a feature of an enantioselective desymmetrisation reaction in which a kinetic resolution of the products is also occurring. An asymmetric Grignard cross-coupling carried out with racemic monotriflate **115** was investigated. At 20% conversion to diphenyl product **116**, the recovered **115** was enantiomerically enriched

((*S*)-isomer of 17% ee) indicating that a kinetic process occurs in which the (*R*)-isomer of **115** undergoes the phenylation about five times faster than its (*S*)-isomer.

The monophenylated product **115**, was readily made enantiomerically pure with high recovery by simple recrystallisation and was further used to prepare enantiomerically pure monophosphine ligands containing axial chirality. The monotriflate **115** was substituted with a diphenylphosphino group in the presence of $Pd(OAc)_2$+dppp in DMSO followed by reduction of the diphenylphosphinyl group with trichlorosilane and triethylamine to give the chiral triaryl monophosphine (*S*)-**119** (Figure 15). This chiral monophosphine was found to be more efficient than MeO-MOP (whose basic skeleton is analogous) in the palladium catalysed asymmetric hydrosilylation of styrene with trichlorosilane affording the product in 91% ee.



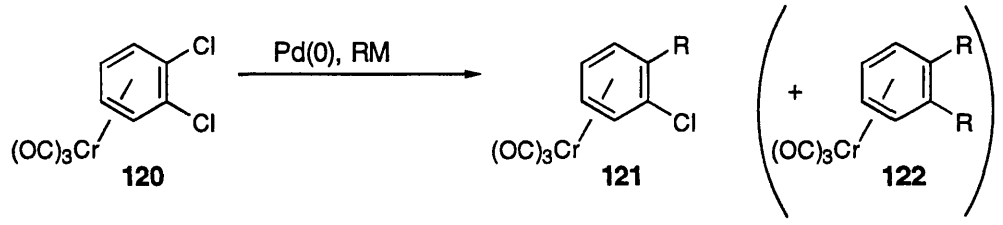
(S)-**119**

Figure 15

Suzuki cross-coupling reactions

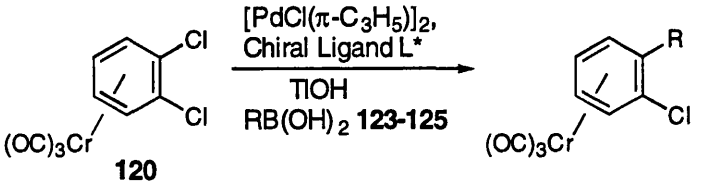
Uemura and Hayashi have described the palladium catalysed asymmetric cross-coupling of *meso* tricarbonyl (*o*-dichlorobenzene) chromium complexes with alkenyl and arylboronic acids.[97] The chloroarene substrates are not widely used in palladium chemistry because the oxidative addition of the C-Cl bond is usually difficult, however the coordination of the arene ring with an electron withdrawing tricarbonylchromium

group was shown to facilitate the oxidative addition step of the chlorine-carbon bond to palladium.[98,99] The substitution of one of the two enantiotopic chlorine atoms in the *meso* chromium substrate **120** delivers a tricarbonyl (η^6-arene)chromium complex **121** which exists in two enantiomeric forms due to planar chirality; the arene now being *ortho* substituted with two different groups (Scheme 20).



Scheme 20

The achiral substrate **120** was desymmetrised in palladium catalysed Suzuki coupling reactions employing a range of chiral ligands. Selected results are presented in Table 6. The use of a palladium catalyst coordinated with ferrocene type ligand (*S*)-(*R*)-PPFA **37** in the Suzuki coupling of **120** with either aryl or alkenyl boronic acids resulted in the formation of the monosubstituted product with the highest enantiomeric excess. Among the boron reagents employed, the arylboronic acid **125** showed the highest enantioselectivity in the cross-coupling reactions (up to 69% ee).

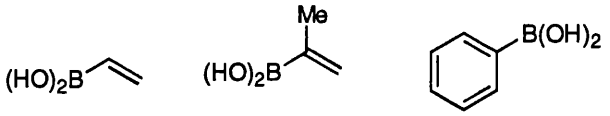


126 R = CH_2=CH
127 R = CH_2=CMe
128 R = C_6H_5

Table 6: Enantioselective desymmetrisation of *meso* chromium substrate **120**

Entry	Boronic acid[a]	Chiral Ligand L*	°C, h	monosubstituted Product (yield %)	ee (%) (abs. conf.)
1	**123**	(*S*)-(*R*)-**37**	23, 48	**126** (43)	38 (1*S*, 2*R*)
2	**124**	(*S*)-(*R*)-**37**	27, 48	**127** (61)	44 (1*S*, 2*R*)
3	**124**	(*R*)-**4**	35, 48	**127** (44)	25 (1*S*, 2*R*)
4	**125**	(*S*)-(*R*)-**37**	28, 18	**128**(16)	49 (1*S*, 2*R*)
5	**125**	(*S*)-(*R*)-**37**	50, 18	**128** (40)	69 (1*S*, 2*R*)

[a] molar ratio complex **120**/boronic acid/chiral ligand L*/palladium = 1.0/3.0/0.12/0.10

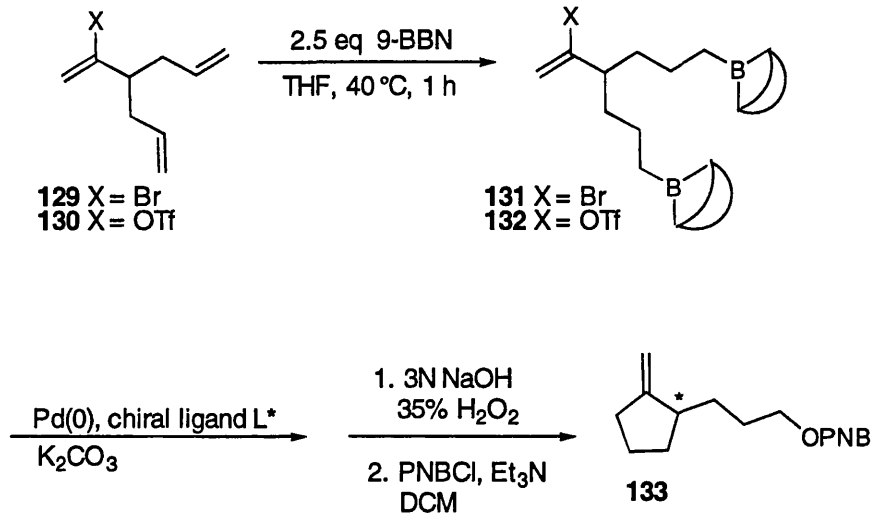


123 **124** **125**

The authors also attempted an asymmetric Stille coupling and an enantioselective Grignard cross-coupling of *meso*- tricarbonyl (*o*-dichlorobenzene) chromium complex **120** and found, interestingly, that the enantioselectivity largely depends on the metal of the vinylating or arylating reagents; with the stannane reagents, the monocoupling product resulted in racemic compound while organozinc reagents gave coupling products with moderate enantioselectivity (up to 42% ee). Thus Uemura and Hayashi proposed that the oxidative addition step would occur enantioselectively with the complex reagents derived from palladium / chiral phosphine / vinylating metal and not with the simple chiral palladium reagents.

Recently Shibasaki *et al* reported the first intramolecular Suzuki coupling of prochiral alkylboron reagents.[100] The authors' strategy involved enantiotopic group selective ring closure of the prochiral triflate **132** and bromide **131** generated *in situ* from achiral

dienes **130** and **129** by treatment with 9-BBN in THF. This closure catalysed by a palladium complex with an asymmetric ligand would lead, after oxidative work-up with basic hydrogen peroxide and protection of the alcohol functionality, to the optically active cyclopentane derivative **133** (Scheme 21).



Scheme 21

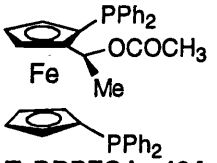
A range of chiral phosphine ligands were investigated in the asymmetric intramolecular Suzuki coupling of prochiral dialkyl boranes (Table 7). The use of (*R*)-BINAP gave no product **133**. However the use of monodentate ligands[101] such as (*R*)-MeO-MOP and (*R*)-OH-MOP resulted in the formation of cyclopentane **133** in good yields albeit with low ee's (up to 14% ee). The bidentate ferrocenyl ligand (*S*)-(*R*)-BPPFOAc[102] **134** generates a palladium catalyst which effects the desymmetrisation of the prochiral dialkylborane substrate and provides the substrate **133** with the highest (still moderate) optical purity of 28%.

When the bromine substrate was employed less satisfactory results were obtained for the asymmetric coupling.

Table 7: Enantioselective desymmetrisation of *meso* dialkylboranes

Entry	substrate[a]	chiral ligand L*	yield of **133** (%)	ee of **133** (%) (abs. conf.)
1	**129**	(*S*)-(*R*)-**134**	41	10 (*S*)
2	**129**	(*R*)-**4**	trace	-
3	**129**	(*R*)-(*S*)-**37**	48	20 (*S*)
4	**130**	(*R*)-**118**	67	14 (*S*)
5	**130**	(*S*)-(*R*)-**137**	58	28 (*R*)

[a] Unless otherwise stated, reactions were carried out by using 10 mol% $Pd_2(dba)_3$, 20 mol% ligand, 5 mol eq of K_2CO_3, 40 °C.

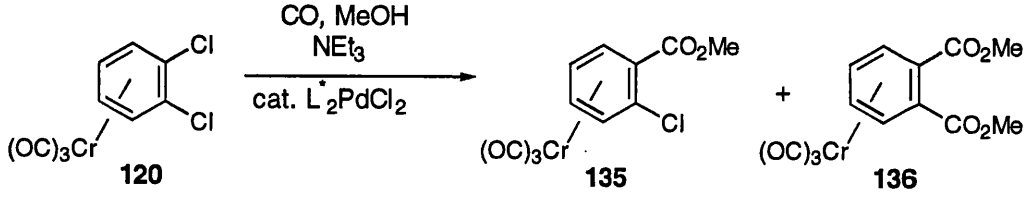


(*S*)-(*R*)-BPPFOAc **134**

The methodology was also extended to substrates containing quaternary carbon atoms; similar levels of enantioselectivity were obtained.

Carbonylation reactions

Very recently the palladium catalysed desymmetrisation of 1,1-dichlorobenzene tricarbonylchromium (0) **120** was achieved employing a methoxycarbonylation reaction.[103] The monocoupled product **135** could be formed in up to 95% ee, along with various amounts of dicoupled product **136** (Scheme 22).



Scheme 22

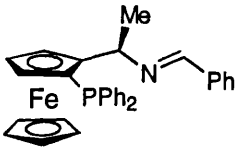
When diphosphine (*R*)-BINAP **4** or ferrocenyl ligand (*S*)-(*R*)-PPFA **37** were used, the monosubstituted product **135** was formed in moderate yield and poor optical purity

(Table 8, Entries 1 and 2). The methoxycarbonylation of substrate **120** with other easily accessible chiral ferrocene *P,N* ligands **137**[104] and **138**[105] provided the product **135** with low enantioselectivity of 2 and 6% ee respectively. However the use of (*R*)-(*S*)-PPF-pyrrolidine **139**[106], a more hindered analogue of PPFA ligand, in carbonylation of **120** delivered the expected product **135** in 63% ee (Entry 5). With 2 mol% of the catalyst (**139**-$PdCl_2$) the product was obtained in 95% ee (31% yield) after 3 h together with 48% of dicoupled material **136** (Entry 6).

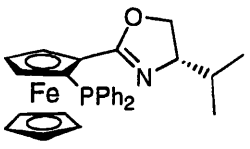
Table 8: Enantioselective carbonylation of substrate **120** [a]

Entry	catalyst	yield of **120** (%)	yield of **135** (%)	yield of **136** (%)	ee (%) of **135** (abs. conf.)
1	(*R*)-**4**-$PdCl_2$	35	49	10	16 (1*R*)
2	(*R*)-(*S*)-**37**-$PdCl_2$	18	41	31	30 (1*R*)
3	(*R*)-(*S*)-**137**-$PdCl_2$	42	43	14	<2
4	(*R*)-(*S*)-**138**-$PdCl_2$	76	22	1	6 (1*R*)
5	(*R*)-(*S*)-**139**-$PdCl_2$	24	47	23	63 (1*S*)
6	(*R*)-(*S*)-**139**-$PdCl_2$ [b]	5	31	48	95 (1*S*)

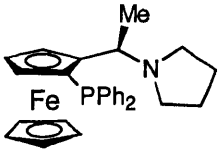
[a] Reactions were performed on 0.5 mmol scale, 2/1 mixture of MeOH/TEA, 5 mol% of palladium catalyst, 1 atm CO at 60 °C for 2 h. [b] Reaction was performed with 2 mol% of catalyst for 3 h.



(*R*)-(*S*)-**137**



(*S*)-(*S*)-*i*Pr-Phosferrox **138**



(*R*)-(*S*)-PPF-pyrrolidine **139**

A novel enantioselective desymmetrisation approach to stereogenic carbon centres

We wanted to develop a new enantioselective desymmetrisation reaction employing palladium catalysed chemistry which would deliver highly enantiomerically enriched products with useful synthetic application. Crucially, our aim was to generate

stereogenic carbon centres, not chiral planes or axes. Attention was first focused on the design of potential symmetrical substrates for such reactions.

The starting materials must contain two identical enantiotopic leaving groups (halogen or triflate) which are capable of undergoing oxidative addition with Pd(0) and which will be differentiated during this step. In order to achieve an enantioselective reaction it is desirable to have one face of the compound very hindered so that it is more difficult to approach than the other. We proposed that the presence of bulky substituents in the vicinity of the leaving groups would enhance the enantiotopic discrimination since the oxidative addition has been shown to be sensitive to steric environment.[107] Finally, the elected *meso*-dihalo (or triflate) compounds must be easily prepared in a short synthesis.

We selected two different families of substrate fulfilling all the criteria presented above. The first substrates were 1,1-dibromoalkenes **140** featuring a *cis*-[3.3.0]octane skeleton and which have a plane of symmetry (Figure 16).

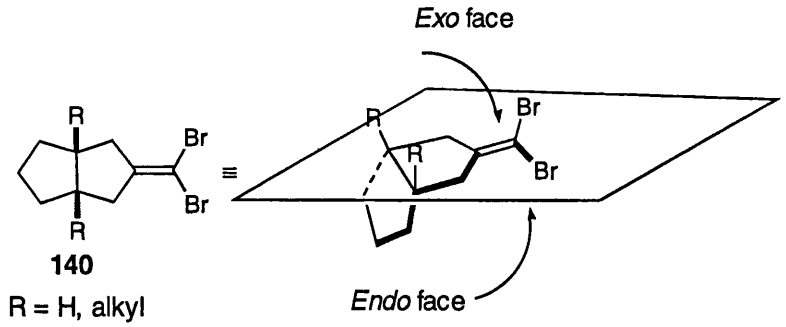
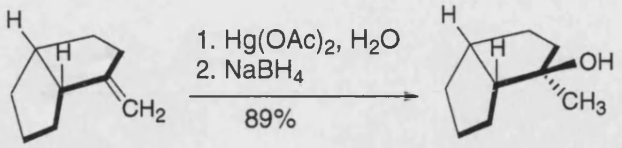


Figure 16

In this type of compound , the face labelled *endo* is more hindered than the *exo* face so that the approach of any catalyst should be easier from the *exo* face. These bicyclic compounds with an attractive U-shape have already been shown to selectively engage reagents from the more accessible *exo* face; for example 2-

methylenebicyclo[3.3.0]octane **141** undergoes rapid oxy-mercuration to give predominantly the *exo*-alcohol **142** (89% yield) (Scheme 23).[108]



141 **142**

Scheme 23

In the catalytic cycle of palladium coupling reactions, the initial catalyst-vinyl halide interaction is reported to be the formation of a η^2 complex prior to oxidative addition.[109] With a bicyclic compound such as **140** the η^2 complex should form by an approach of the catalyst complex from the more sterically accessible alkene stereoface (Figure 17).

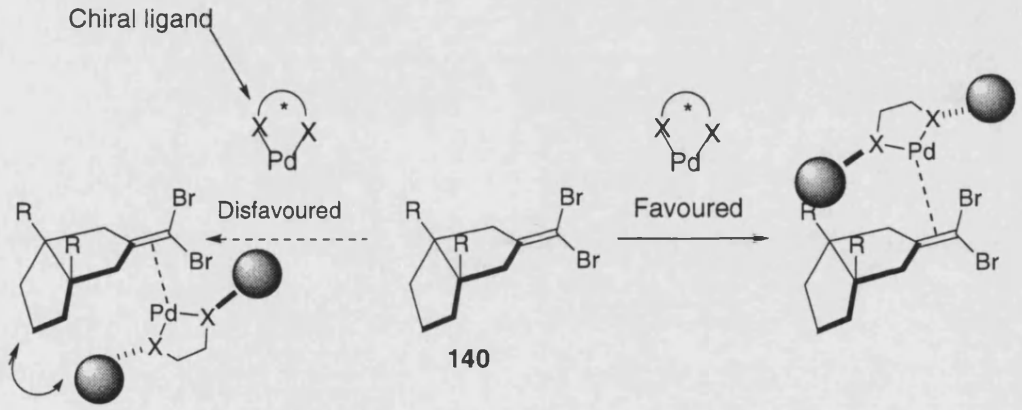
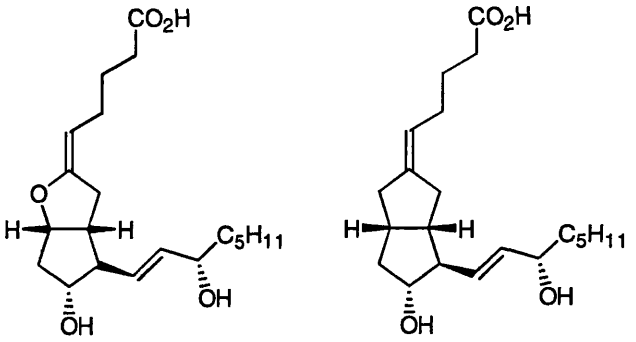


Figure 17

The reaction should then proceed with the oxidative addition of palladium across the more accessible carbon-bromine bond. For these substrate-catalyst systems, oxidative addition across one of the two enantiotopic carbon-halide bond should represent a favoured case while addition across the alternative bond will be non-favoured (steric hindrance of the substituents on the bridge). If efficient enantiotopic group

discrimination is achieved then the products from such a cycle would be enantiomerically enriched.

The products of such a system will be chiral by virtue of containing stereogenic carbon atoms and not by the presence of chiral axes. Enantioselective desymmetrisation of these *cis*-bicyclo[3.3.0]octane compounds would provide a new entry to the skeleton of carbacyclin **143** which is a structurally modified analogue to the potent inhibitor and vasodilator prostacyclin **144** (Figure 18).



143
prostacyclin

144
carbacyclin

Figure 18

For the synthesis of enantiomerically enriched **144** several kinds of enantiomerically enriched starting materials such as resolved derivatives of cyclobutanone,[110] Corey lactone,[111] and a monoacetal of bicyclo[3.3.0]octan-3,7-dione have been employed.[112] An innovative method for the preparation of chiral **144**, including an enantioselective palladium catalysed desymmetrisation process as a key step, could be considered as described in Figure 19.

The *meso* 1,1-dibromoalkene **147** could be desymmetrised *via* an enantioselective Suzuki cross-coupling with protected boronic acid indicated and a chiral palladium catalyst to give the mono-bromide **146**. The bromine atom remaining in **146** can undergo a palladium catalysed reduction employing the stannane reagent tributyltin

hydride in a polar aprotic solvent (such as NMP). Acid catalysed deprotection of the acetal function and functionalisation at the α–position of the ketone moiety should deliver the optically active target molecule carbacyclin **144**.

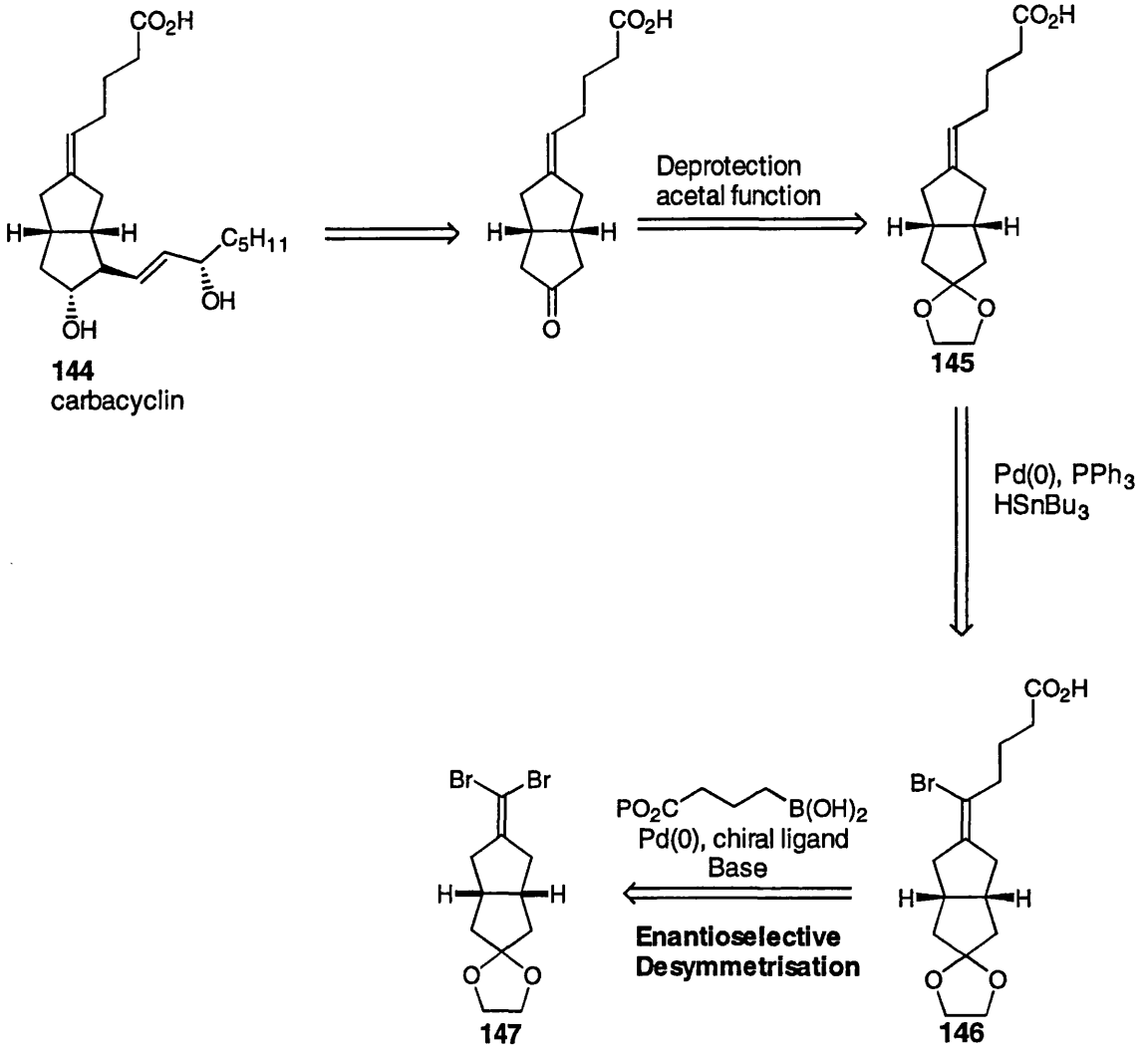


Figure 19

The second class of substrates selected were carbocyclic 2-methyl-2-alkyl-1,4-divinyltriflates such as **148** (Figure 20). These compounds possess a quaternary carbon centre which is included in the plane of symmetry of the molecules. The difference in size of the two substituents situated in position 2 on the cycle will play an important

role in the enantioselectivity of the catalysed reactions. If the substituent R is bulky (in comparison with the methyl group), then the face containing the methyl will appear less hindered and thus more accessible than the alternative face.

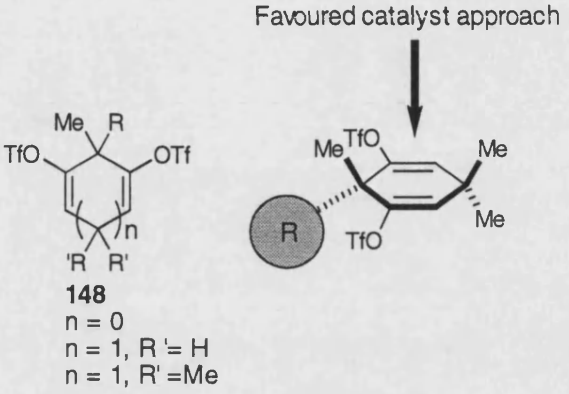


Figure 20

The monosubstituted products generated from palladium cross-coupling reactions could be useful intermediates for natural product or drug syntheses; the remaining triflate group can be reduced to the alkene which could be further functionalised through, for example, epoxidation, hydroxylation or hydroboration (Figure 21).

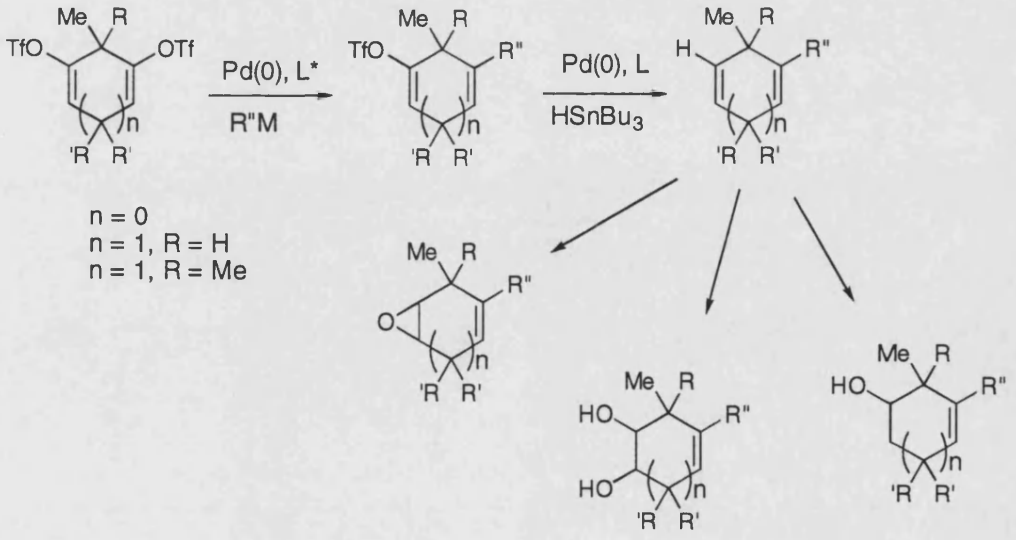


Figure 21

A library of compounds could be created just by varying the substituent in position 2 of the cyclic ring ; a range of compounds with different sized substituents would provide useful information about the enantioselectivity of their palladium catalysed reactions.

Conclusions

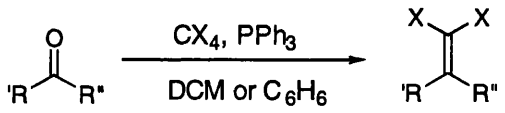
The advantages of desymmetrisation are numerous; it is possible to create one or more chiral stereocentres in a single step, it can be applied to a wide range of substrates and can be used as a key step to deliver synthetically useful compounds. The benefits of the method have now been well recognised and attention is now focused on catalytic versions of this powerful strategy. The efficient use of palladium catalysts in enantioselective desymmetrisation was demonstrated a few years ago. Our interest is to achieve the desymmetrisation of *meso* 1,1-dibromoalkenes and achiral cyclic 1,4-divinyltriflate compounds employing palladium catalysed cross-coupling reactions to deliver enantiomerically enriched potential key intermediates for drug or natural product synthesis. The following chapter will be devoted to the desymmetrisation of 1,1-dibromoalkene substrates; we first present literature precedents about palladium catalysed cross-coupling reactions of 1,1-dibromoalkenes. We then consider the reactivity of selected substrates **140** in Suzuki, Grignard and Stille couplings employing achiral palladium catalysts and finally investigate the enantioselective desymmetrisation of 1,1-dibromoalkene starting materials **140** in Suzuki cross-coupling reactions.

Chapter 3: The preparation and reactivity of 1,1-dibromoolefin substrates in palladium catalysed coupling reactions

Introduction

1,1-Dibromoalkenes have been utilised in various synthetic transformations; historically they have been valuable intermediates for the synthesis of acetylenes from aldehydes or ketones.[113] More recently 1,1-dibromoolefins have been used as electrophiles in palladium catalysed coupling reactions. In particular, palladium mediated reactions of 1,1-dihaloalkenes where one of the C-X bonds participates in the coupling reaction, produce functionalised tri-substituted alkenes.[114]

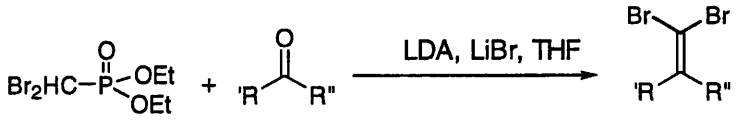
Several "named" reactions can be carried out to prepare these *gem*-dihaloalkene compounds. They can be obtained by olefination of the corresponding ketones *via* one of two main methods. The first scheme follows the procedure presented by Ramirez-McKelvie/Corey-Fuchs (Scheme 24) which utilises a (tribromomethyl) triphenylphosphonium adduct to afford a stabilised dibromomethylide.[115,116] This intermediate is able to act as a nucleophile in the reaction with ketones or aldehydes.



R', R" = alkyl and/or allyl
X= I, Br

Scheme 24

The second method (Savignac-Coutrot) employs the diethyl dibromomethane-phosphonate anion in the presence of LiBr in the reaction with the carbonyl compounds (Scheme 25).[117]



R', R" = alkyl and/or allyl

Scheme 25

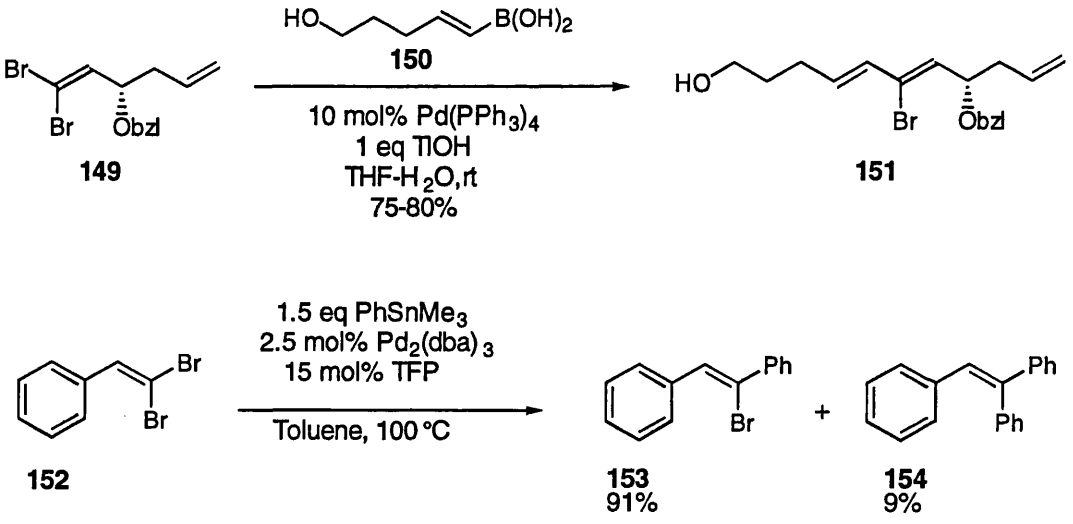
The synthesis of a family of *gem*-dibromovinylidene intermediates has been realised from 1-bromoalkynes *via* a modified version of Zweifel's method. This uses 9-BBN as the hydroborating reagent to replace disiamylborane, followed by mono-oxidation with triethylamine *N*-oxide and bromination.[118] However, Corey-Fuchs dibromo methylenation is the method most commonly employed to deliver the expected dibromoalkene products, generally in good to excellent yields.

1,1-Dibromoololefin compounds have been reported to couple efficiently in palladium catalysed cross-coupling reactions employing stannane reagents,[119,120] boronic acids,[121,122], boronic esters, zinc species[123,124] and substituted alkenes or alkynes. In most cases, the monosubstituted (*Z*)-1-bromo-1-alkene isomers are formed preferentially. The high selectivity of the palladium catalysed reactions may be due to the oxidative addition as a key step where Pd(0) is inserted into the less sterically hindered carbon bromine bond.[125]

For example, the Suzuki-Miyaura coupling reaction of dibromoalkene **149** with vinyl boronic acid **150** in the presence of the base TlOH[126] at room temperature delivered the (*Z*,*E*)-2-bromo-1,3-diene product **151** in 75-80% yield (Scheme 26).[107] These TlOH conditions, first described by Kishi and co-workers,[127,128] are compatible with a wide range of potentially base sensitive functionalities such as unprotected aldols, stereocentres *alpha* to methyl ketones and carboalkoxyl groups. The first Suzuki reactions successfully carried out with 1,1-dibromoalkenes employed the toxic base

TlOH, however there have been recent examples reported where couplings occur with alternative bases such as Na_2CO_3 or NaOH.[129,130]

(*Z*)-1-Bromo-1-alkene can also be prepared in good yields *via* a Stille coupling of vinylidene dibromides with a variety of tin compounds. Thus the coupling of β,β-dibromostyrene **152** with trimethylphenyltin in the presence of $Pd_2(dba)_3$ (2.5 mol%) and TFP (15 mol%) in toluene at 100 °C afforded excellent yields of (*Z*)-isomer of monocoupled product **153** (91%) together with a small amount of the dicoupled product **154** (9%) (Scheme 26).[131]



Scheme 26

The use of an *ortho* methoxy group in the dibromide **152** was shown to give the alternative (*E*)-1-bromo-1-alkene isomer; the OMe group chelates the palladium before oxidative addition of the Br-C palladium *cis* to the benzene ring. This attractive chelating strategy was applied to the synthesis of 3-substituted-isocoumarins which display important biological activities.[132] The Stille coupling of 2-(2',2'-dibromovinyl)benzoate **155** with trimethylphenyltin catalysed by a palladium species

(generated from tris(dibenzylideneacetone)dipalladium and tris-(2-furyl)phosphine)) in toluene delivers the expected isocoumarin **158** in 92% yield (Figure 22).

The first step is a Stille reaction of the (*E*)-C-Br bond with the stannane, followed by the oxidative addition of palladium to the (*Z*)-bromide to give intermediate **156**. The coordination of the palladium to the ester group in **156** promotes elimination of methylbromide to give intermediate **157**. Further reductive elimination gives the corresponding isocoumarin **158**.

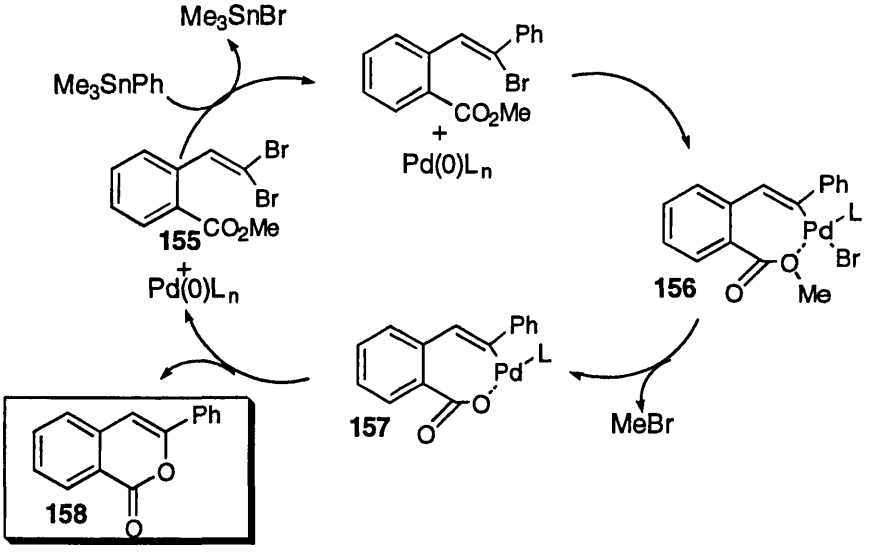
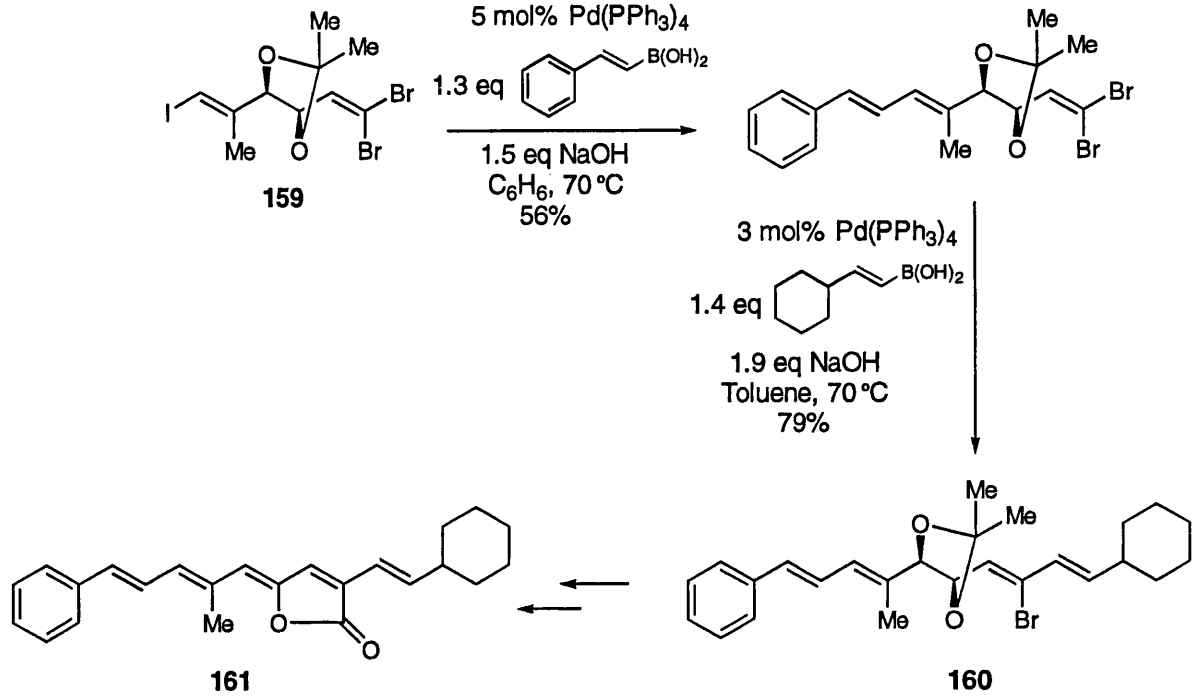


Figure 22

The stereoselective palladium coupling reactions of 1,1-dibromoalkene substrates can be applied to natural product synthesis by delivering conjugated olefins and polyenes often observed in the skeleton of biologically active compounds. Recently a dibromoiododiene unit was employed as an intermediate in the preparation of peridin which plays a central role in the photosynthesis of marine algae. The substrate **159** first underwent a selective Suzuki coupling with a phenyl substituted vinylboronic acid at the less hindered C=C(-H)-I terminus followed by a second palladium coupling step using cyclohexyl-substituted boronic acid and aqueous NaOH to deliver the *cis*-alkene

adduct **160** (Scheme 27). This was further functionalised (5 steps) to give the desired peridin **161** product in overall 20% yield.[133]



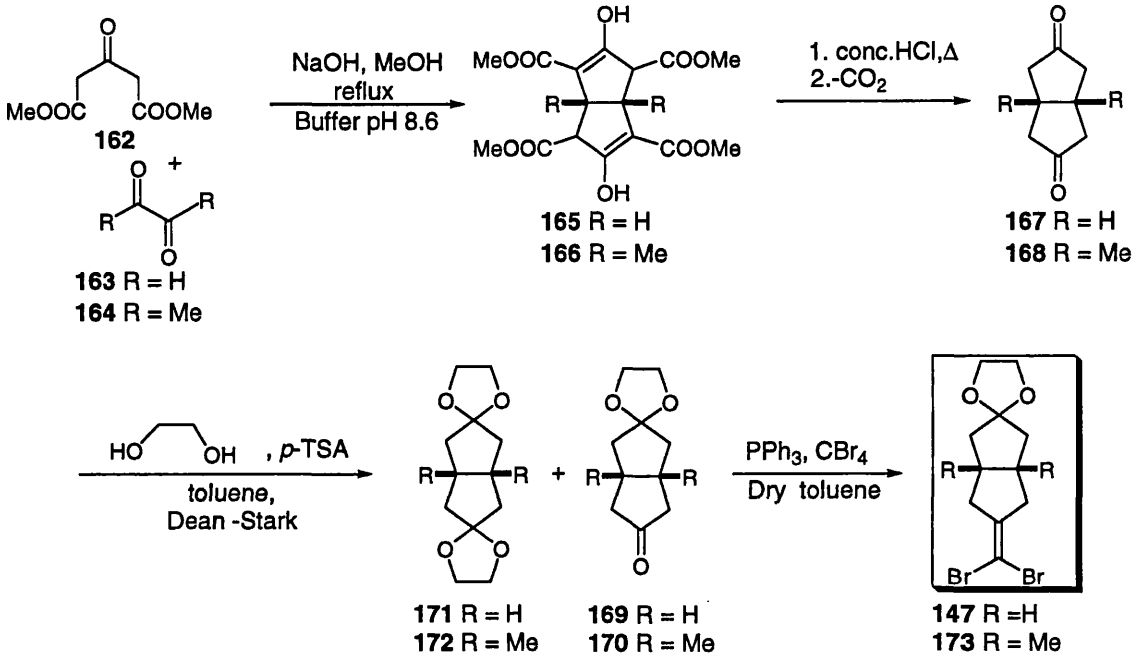
Scheme 27

Reactivity of selected 1,1-dibromoolefin substrates

Preparation of the dibromide starting materials

The 1,1-dibromoalkene substrates **147** and **173** were readily prepared in a four step synthesis (Scheme 28). Starting from dimethyl-1,3-acetonedicarboxylate **162** and either glyoxal **163** (R=H) or 2,3-butanedione **164** ($R=CH_3$) under basic conditions the tetraesters **165** and **166** were formed in good yield (70%).[134] The tetraesters were hydrolysed (concentrated hydrochloric acid and glacial acetic acid) and then decarboxylated (heating) to provide the diketones **167** and **168** in 75-88% yield. Monoprotection of the diketones as an acetal (ethylene glycol, acid)[135] delivered a

mixture of diketone, ketoacetal **169** or **170** and diacetal **171** or **172** (1:2:1). Finally, these ketoacetal moieties **169** or **170** can undergo a dibromomethylenation by Corey-Fuchs protocol using carbon tetrabromide and triphenylphosphine in toluene at reflux to give the desired 1,1-dibromoalkenes **147** and **173** in 65%-68% yield from the ketone.[136]



Scheme 28

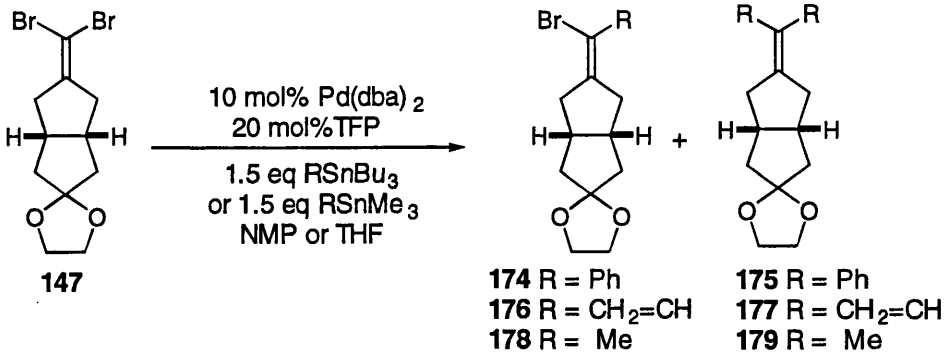
Two substrates have been synthesised; one where R = H and another one where R = Me, in order to examine the influence of the methyl groups on the enantioselectivity when compared to hydrogen atoms.

The reactivity of the two dibromide starting materials was first studied in catalysed palladium reactions employing achiral phosphine ligands. The reactions selected for the couplings were Stille cross-couplings, Grignard cross-couplings and the Suzuki-Miyaura reaction.

Reactivity of the 1,1-dibromoalkene substrates in palladium catalysed reactions with racemic catalysts

Stille coupling reactions

When the dibromide **147** was reacted with a tin compound in presence of a palladium catalyst two products were observed; one compound derives from the substitution (with an alkyl or aryl group) of one bromine atom and the second product corresponds to both bromine atoms being substituted (Scheme 29).



Scheme 29

The Stille reactions with substrate **147** were performed under a variety of conditions (Table 9).[10]

Table 9: Stille coupling of dibromide **147**

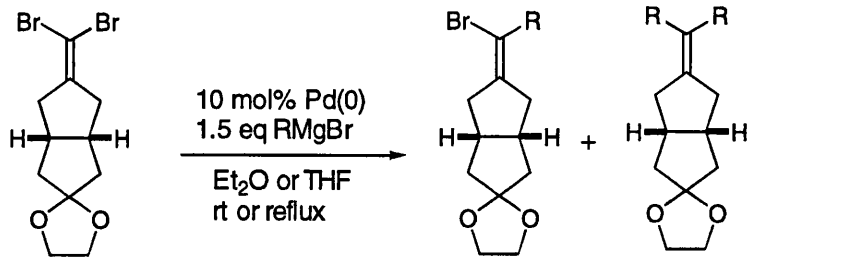
Entry	Tin reagent [a]	solvent, T °C	Time (h)	**147** recovered (%)	Yield of monocoupled product (%)	Yield of dicoupled product (%)
1	Me_4Sn, 1.60 eq	THF, 50	17	100	-	-
2	$Bu_3Sn(CH{=}CH_2)$, 1.25 eq	NMP, 50	12	100	-	-
3[b]	Bu_3SnPh, 1.50 eq	NMP, rt	70	45	-	10
4	Bu_3SnPh, 1.50 eq	NMP, 50	26	16	-	76
5	Me_3SnPh, 1.25 eq	NMP, 50	26	31	-	45

[a] Reactions were carried out with 10 mol% of Pd(dba)2 and 20 mol% of TFP. [b] Reaction was carried out with 40 mol% of TFP.

The reactions performed using tributyl(vinyl)tin and tetramethyltin were found to be unsuccessful. None of the monosubstituted products **176** or **178** or dicoupled products **177** or **179** were observed. However, the use of the more nucleophilic tributylphenyltin or trimethylphenyltin in the Stille coupling of **147** provided the exclusive formation of the dicoupled **175** under a variety of conditions. The formation of monoproduct **174** was not observed indicating that under the reaction conditions it undergoes a second substitution delivering the dicoupled product **175**. The increased reactivity of substituted-1-vinylbromide has been reported in the literature.[130] They noted that when symmetrical 1,1-dibromoolefins are subjected to Suzuki cross-coupling reactions with a wide range of substituted phenylboronic acids, the couplings afforded the formation of 1,1-disubstituted alkenes in quantitative yields.

Grignard cross-coupling reactions

The cross-coupling reaction of dibromide **147** has been explored using phenylmagnesium bromide and vinylmagnesium bromide (Scheme 30).



147

174 R = Ph
176 R = CH=CH$_2$

175 R = Ph
177 R = CH=CH$_2$

Scheme 30

The addition of the Grignard reagent was carried out at 0 °C, before the solution was slowly warmed to room temperature and then either stirred at ambient temperature or heated to reflux (Table 10).

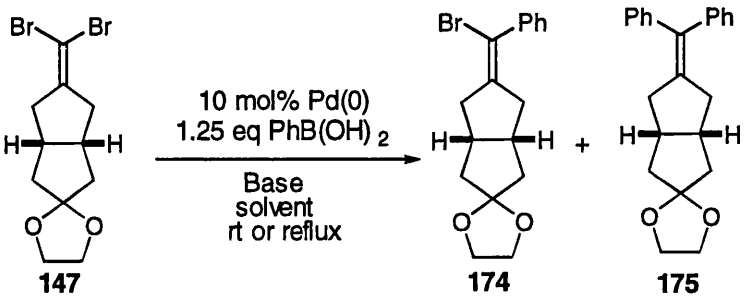
Table 10: Conditions used for Grignard couplings of **147**

Entry	RMgBr	Pd species	L	solvent, T°C	Time (h)	Yield
1	PhMgBr	$Pd(dba)_2$	PPh_3	ether, rt	70	nd
2	PhMgBr	$Pd(dba)_2$	PPh_3	THF, rt	70	nd
3	$(CH_2=CH)MgBr$	$PdCl_2(dppb)$	-	ether, reflux	8	nd
4	PhMgBr	$PdCl_2(dppb)$	-	ether, reflux	8	nd

The catalysed Grignard cross-coupling reactions of **147** at room temperature employing the Pd(0) species ($Pd(dba)_2$) did not allow the formation of any expected products, and only starting material was recovered after work-up. Increasing the reaction temperature did not have any effect on the reactivity of the substrate. Pd(II) catalysts which are known to be efficient Grignard catalysts were investigated next.[137] However, when dibromide **147** was reacted with phenylmagnesium bromide employing $PdCl_2(dppb)$ at reflux in ether a reaction did occur (formation of a new spot below the starting material on tlc). Work-up of the reaction and purification by flash column chromatography gave 32% yield of biphenyl (coupling of two Grignard reagents), along with 52% of recovered starting material and an inseparable mixture of starting material/disubstituted product and/or monosubstituted products (integration of aromatic protons was inbetween 5 and 10 H and there was more than one signal for CH_2-O protons). Attempts to separate these compounds by flash column chromatography with different solvent elution systems failed. The focus was then turned to the Suzuki cross-coupling reactions of *gem*-dibromide **147**. These reactions would hopefully reach completion and would provide the monosubstituted compounds as single products.

Suzuki-Miyaura cross-coupling reactions

The catalysed reactions of dibromoalkene **147** were carried out with phenylboronic acid **125** (1.25 eq). This led to the formation of monosubstituted compound **174** as well as the disubstituted adduct **175** (Scheme 31).



Scheme 31

Various conditions were investigated which included the use of different bases, solvents and palladium catalysts (Table 11):

Table 11: Conditions used for Suzuki couplings of **147** with phenyl boronic acid **125**

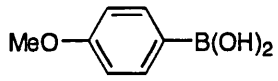
Entry	Pd species	L	solvent, T°C	Base	Time (h)	Yield
1	$Pd(PPh_3)_4$	-	THF/H_2O, rt	TlOH	45	nd
2	$Pd(PPh_3)_4$	-	DME, 80	CsF	12	nd
3	$Pd(dba)_2$	PPh_3	THF/H_2O, rt	KOH	124	nd
4	$Pd(PPh_3)_4$	-	DMA/H_2O, rt	TlOH	8	nd
5	$Pd(dba)_2$	PPh_3	DME, 80	CsF	8	nd

All the conditions outlined in Table 11 provided the 1,1-diphenyl-1-alkene **175** as a single product (Entry 2 and 4) or as a mixture of 1-phenyl-1-bromide-alkene **174** and product **175**. Higher catalyst loading (20 mol% of Pd) was not found to enhance the conversion, however a higher reaction temperature (50 °C) in the presence of TlOH base enabled the reaction to reach completion.

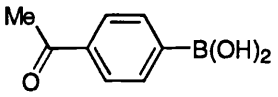
The purification of the mixture of products **174/175** (eventually mixed with starting material) by preparative tlc failed. The diphenylalkene **175** was eventually purified by recrystallisation in hot petroleum-ether leaving a mother liquor still containing a small amount of **175** combined with the monosubstituted product **174** (no ratio could be calculated from ^{1}H NMR of the mother liquor since the spectra were all complex).

The difficulties in purification were probably due to the similar polarities of the starting material and the products. Other boronic acids were then selected which contain polar substituents on the phenyl ring which should increase the polarity of the products and therefore enable easier separation.

Two further commercially available boronic acids have been used; 4-methoxyphenylboronic acid **180** and 4-acetylphenylboronic acid **181.**



180



181

The Suzuki cross-coupling of 1,1-dibromoolefin **147** was first investigated employing boronic acid **180** and was catalysed by $Pd(dba)_2$ or $Pd(PPh_3)_4$ in the presence of CsF or TlOH. The monocoupled product **182** and dicoupled product **183** were formed and easily purified by flash column chromatography on silica gel (Table 12).

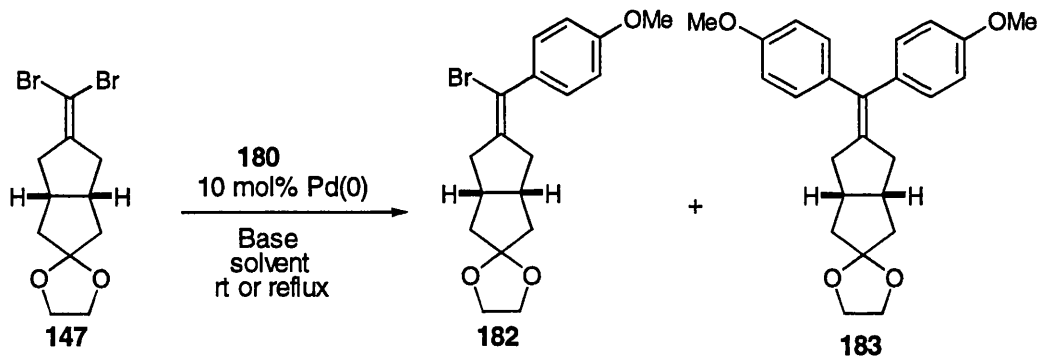


Table 12: Suzuki coupling of dibromide **147** with boronic acid **180** [a]

Entry	equivalent of **180**	Pd(species)	Ligand	Base	solvent, T °C	Yield of **182** (%)	Yield of **183** (%)
1	1.35 eq	$Pd(dba)_2$	P(*o*-tolyl)$_3$	CsF	DME, 80	-	60
2	1.25 eq	$Pd(PPh_3)_4$	-	TlOH	THF/H_2O, rt	15	36
3	1.25 eq	$Pd(PPh_3)_4$	-	TlOH	DMA/H_2O, rt	16	21
4	1.25 eq	$Pd(dba)_2$	dppb	CsF	DME, 80	20	22
5	1.25 eq	$Pd(dba)_2$	dppf	CsF	DME, 80	13	6

[a] The reactions were carried out under nitrogen using either CsF (3 eq) or TlOH (1 eq), palladium catalyst 10 mol% and ligand 10 mol% (bidentate) or 20 mol% (monodentate).

When the Suzuki coupling of dibromide **147** was carried out following the procedure of Wright[138] which first reported the use of caesium fluoride as an efficient base for coupling with organoboron species, the disubstituted product **183** could be isolated (as a single product) in good yield (60%). The monosubstituted product **182** (along with some dicoupled product) could be formed by employing the bidentate phosphine dppb, however the yields of either products were moderate (20% and 22% respectively for **182** and **183**). The use of aqueous thallium hydroxide base in the coupling of **147** at room temperature resulted in lower yields of both products **182** and **183**. None of the conditions attempted for the coupling reaction of **147** with arylboronic acid **180** allowed the exclusive formation of monosubstituted product **182** which may be due to the relatively high reactivity of the mono-bromide derivatives towards Suzuki conditions.

The use of arylboronic **181** substituted with an electron withdrawing group in a *para* position was found to effect the Suzuki coupling of **147** delivering the products **184** and **185** (Table 13). The lower nucleophilicity of the boronic acid **181** (because of the electron- withdrawing group in the *para* position on the ring) could be responsible for the lower observed yields of mono and dicoupled products.

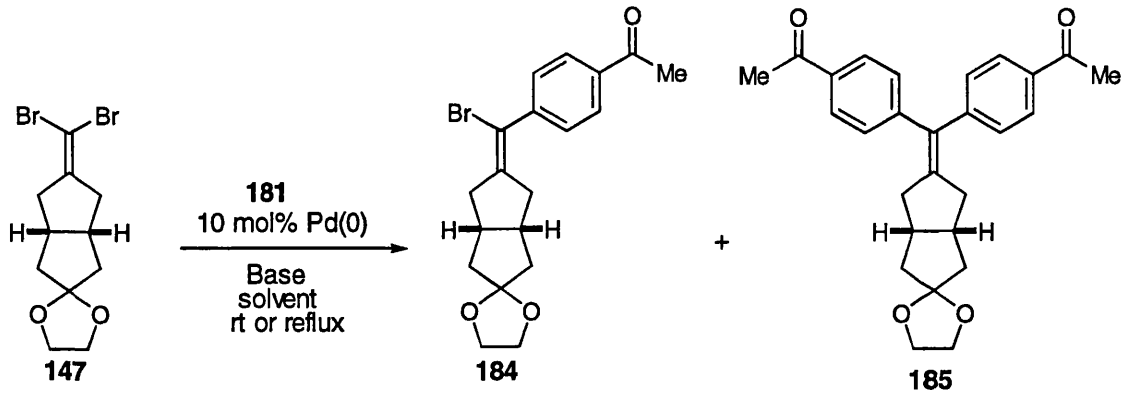


Table 13: Suzuki coupling of dibromide **147** with boronic acid **181** [a]

Entry	equivalent of **181**	Pd species	Ligand	Base	solvent, T °C	Yield of **184** (%)	Yield of **185** (%)
1	1.25 eq	$Pd(PPh_3)_4$	-	TlOH	THF/H_2O, rt	16	20
2	1.25 eq	$Pd(PPh_3)_4$	-	TlOH	DMA/H_2O, rt	8	7
3	1.25 eq	$Pd(dba)_2$	dppb	CsF	DME, 80	12	13

[a] The reactions were carried out under nitrogen using either CsF (3 eq) or TlOH (1 eq), palladium catalyst 10 mol% and ligand 10 mol% (bidentate) or 20 mol% (monodentate).

The use of aqueous thallium hydroxide in THF at room temperature was found to deliver the monosubstituted product **184** with the highest yield (16%), but this was still only moderate. The use of DMA as a solvent combined with the strong base TlOH has been reported to be an efficient reagent system for the Suzuki cross-coupling of aryliodides with phenyl boronic acid.[139] However the coupling of **147** with phenylboronic acid **181** under these conditions gave the expected products **184** and **185** again in poor yields (8 and 7% respectively).

The reactivity of dimethylated dibromoalkene **173** in Suzuki coupling with phenylboronic acids **180** and **181** was also investigated. The range of yields obtained for the mono and dicoupled products using either of the boronic acids cited was comparable to the range of yields observed in the coupling of dibromide **147** (Table 14).

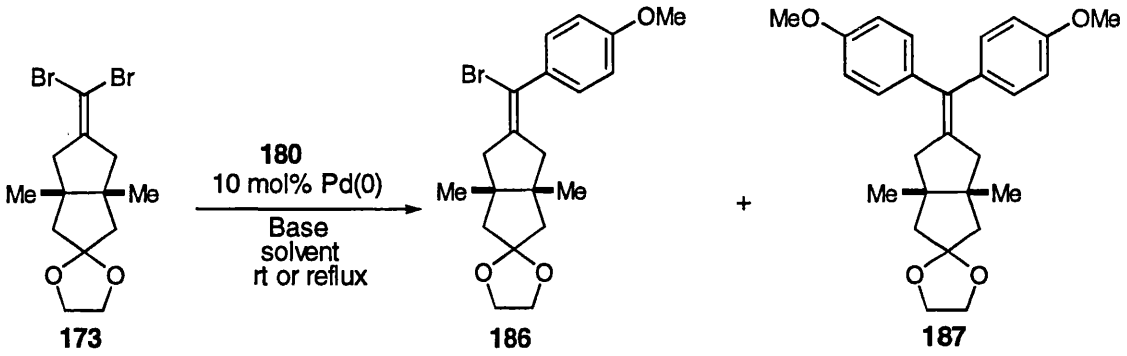


Table14: Suzuki coupling of dibromide **173** with boronic acid **180** [a]

Entry	equivalent of **180**	Pd(species)	Ligand	Base	solvent, T °C	Yield of **186** (%)	Yield of **187** (%)
1	1.25 eq	$Pd(dba)_2$	P(*o*-tolyl)$_3$	CsF	DME, 80	7	16
2	1.25 eq	$Pd(PPh_3)_4$	-	TlOH	THF/H_2O, rt	12	4
3	1.25 eq	$Pd(dba)_2$	dppb	CsF	DME, 80	14	32

[a] The reactions were carried out under nitrogen using either CsF (3 eq) or TlOH (1 eq), palladium catalyst 10 mol% and ligand 10 mol% (bidentate) or 20 mol% (monodentate).

The use of CsF in DME at 60 °C was found to give a very poor yield of 1-bromo-1-phenyl compound **186** along with a small amount (16% yield) of dicoupled product **187**. Higher conversion could be reached with the bidentate ligand dppb providing an overall combined yield of products (**186** and **187**) of 46%.

Finally, the Suzuki coupling of dibromide **173** with 4-acetylphenylboronic acid **181** was explored (Table 15).

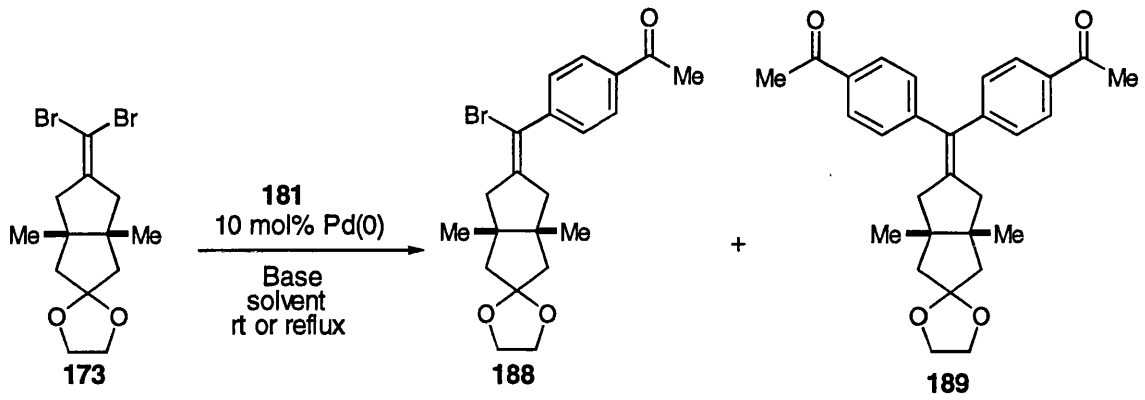


Table 15: Suzuki coupling of dibromide **173** with boronic acid **181** [a]

Entry	equivalent of **181**	Pd(species)	Ligand	Base	solvent, T °C	Yield of **188** (%)	Yield of **189** (%)
1	1.25 eq	$Pd(PPh_3)_4$	-	TlOH	THF/H_2O, rt	22	7
2	1.25 eq	$Pd(dba)_2$	dppb	CsF	DME, 80	13	23

[a] The reactions were carried out under nitrogen using either CsF (3 eq) or TlOH (1 eq), palladium catalyst 10 mol% and ligand 10 mol% (bidentate) or 20 mol% (monodentate).

Both conditions employed for the coupling of dibromide **173** gave moderate yields of monosubstituted product **188** and disubstituted compound **189**. However the use of the aqueous base TlOH seemed to inhibit the formation of the dicoupled product.

Our aim was to achieve the desymmetrisation of both dibromide substrates **147** and **173** by forming enantiomerically enriched monocoupled products. The best conditions to prepare the compounds **182, 184, 186** and **188** in moderate to good yields were found to be:

-$Pd(dba)_2$ 10 mol%, P(*o*-tolyl)$_3$ 20 mol%, CsF (3 eq), DME, 60 °C, 24 h

-$Pd(PPh_3)_4$ 10 mol%, TlOH 1 eq, THF-H_2O, rt, 12h.

However, the first set of conditions requires heating which has been shown in many cases to lower enantioselectivity. The Suzuki coupling of dibromide **147** was carried out with boronic acid **180** in the presence of CsF (3 eq), $Pd(OAc)_2$ and triphenylphopshine in dioxane, DME, or THF at room temperature. This allows the formation of the products **182** and **184** with slightly lower yields (11 and 17% yield respectively). Under these selected conditions the enantioselective desymmetrisation of dibromide **147** and **173** in the presence of various chiral palladium catalysts was investigated.

Enantioselective desymmetrisation of 1,1-dibromoalkene substrates

The enantioselective desymmetrisation of 1,1-dibromide **147** was first investigated. The chiral palladium catalysts were formed *in situ* employing either $Pd(dba)_2$ or $Pd(OAc)_2$ and a mono or a bidentate chiral ligand. The enantiomeric excess of the monoproducts was determined by HPLC. Table 16 lists the results using 4-methoxyphenylboronic acid **180**.

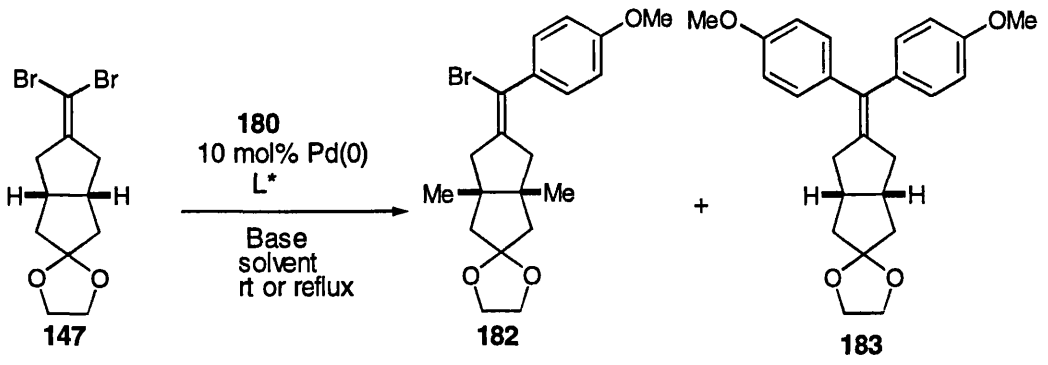
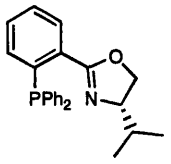


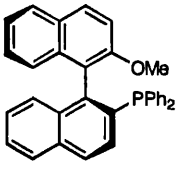
Table 16: Asymmetric Suzuki coupling of dibromide **147** with boronic acid **180** [a]

Entry	Pd(species)	Ligand	solvent, T°C	Yield of **182**(%)	Yield of **183** (%)	ee[b] of **182** (%)
1	$Pd(OAc)_2$	(*S*)-**104**	DME, 80	-	-	-
2	$Pd(OAc)_2$	(*S*)-**104**	dioxane, rt	<10	28	8
3	$Pd(dba)_2$	(*S*)-**190**	DME,80	<10	11	0
4	$Pd(OAc)_2$	(S)-**118**	dioxane,rt	19	19	2
5	$Pd(dba)_2$	(S)-**118**	dioxane, rt	<10	<10	10

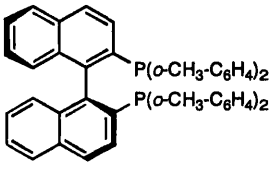
[a] The reactions were carried out under nitrogen using CsF (3 eq) , palladium catalyst 10 mol% and ligand 10 mol% (bidentate) or 20 mol% (monodentate).[b] Enantiomeric Excess was determined by HPLC (chiralcel OD column).



(*S*)-*i*-Pr-PHOX **104**



(*S*)-MeO-MOP **118**



(*S*)-Tol-BINAP **190**

The *P,N* ligand *i*-Pr-PHOX **104** when used in combination with $Pd(dba)_2$ was found to form an inactive chiral catalyst, however when $Pd(OAc)_2$ was exchanged for $Pd(dba)_2$ both monocoupled **182** and dicoupled product **183** were obtained in moderate yields and poor enantioselectivity for **182** (Entry 2). The best conversions were achieved with the monodentate phosphine ligand (*S*)-MeO-MOP **118**. However disappointing enantioselectivity for monocoupled **182** (Entry 4) was obtained. The ability of monodentate ligands to deliver good yields of products but low enantioselectivity has been observed in enantioselective desymmetrisation studies reported recently.[100]

The enantioselective desymmetrisation of substrate **147** with 4-acetylphenylboronic acid **181** was also investigated (Table 17).

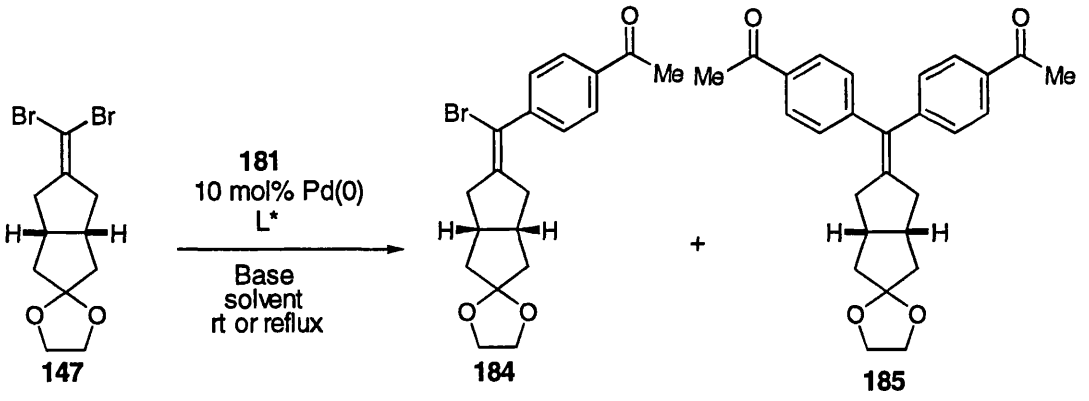
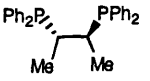


Table 17: Asymmetric Suzuki coupling of dibromide **147** with boronic acid **181** [a]

Entry	Ligand	Base	solvent, T°C	Yield of **184** (%)	Yield of **185** (%)	ee[b] of **184** (%)
1	(*S,S*)-**191**	CsF	DME, 80	4	8	8
2	(*S*)-**118**	TlOH	THF/H_2O, rt	5	8	6
3	(*S*)-**118**	CsF	dioxane, rt	5	13	8

[a] The reactions were carried out under nitrogen using CsF (3 eq) or TlOH (1 eq), Pd(dba)2 10 mol% and ligand 10 mol% (bidentate) or 20 mol% (monodentate). [b] Enantiomeric Excess was determined by HPLC (chiralcel OD column).



(*S,S*)-CHIRAPHOS **191**

The range of enantiomeric excess obtained utilising arylboronic acid **181** was comparable with the enantiomeric excess achieved when arylboronic acid **180** was employed. The highest enantioselectivity of 10% was reached when the reaction was carried out with chiral ligand (*S*)-MeO-MOP **118** in the presence of CsF in dioxane at room temperature.

Having demonstrated a poorly enantioselective desymmetrisation could be achieved on dibromide **147**, we hoped the extra methyl groups present in dibromide **173** might increase the enantioselectivity. We speculated that, during the oxidative addition, the

interactions between the methyl groups and the substituents on the palladium catalyst might be greater and thus provide a more selective reaction (Figure 23).

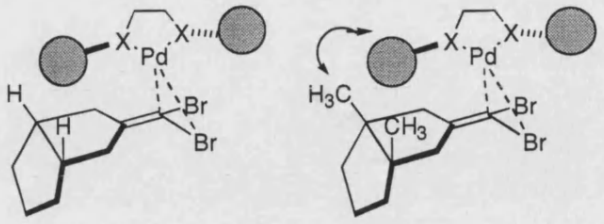


Figure 23

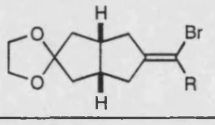
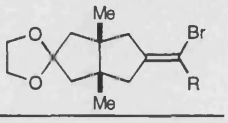
Enantioselective desymmetrisation reactions on substrate **173** were carried out with both boronic acids **180** and **181** in the presence of:

-10 mol% $Pd(OAc)_2$, 10 mol% (*S*)-*i*-Pr-PHOX, 1.25 eq boronic acid (Method A)

-10 mol% $Pd(dba)_2$, 20 mol% (*S*)-MeO-MOP, 1.25 eq boronic acid (Method B)

The results employing successively these two methods and the two different dibromide substrates **147** and **173** are presented in Table 18.

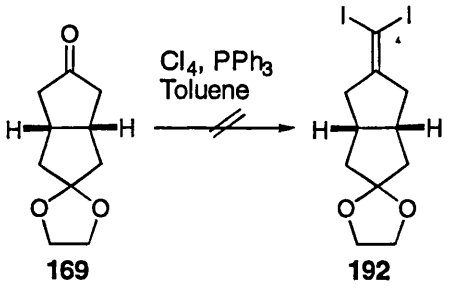
Table 18: Compared enantioselectivity of sustrate **147** and **173** in Suzuki cross-coupling reactions[a]

Conditions		
$Pd(OAc)_2$ + *i*-Pr-PHOX *o*-MeO-$C_6H_4B(OH)_2$	yield: 2% ee: 8%	yield: <1% ee: 13%
$Pd(OAc)_2$ + *i*-Pr-PHOX *o*-MeCO-$C_6H_4B(OH)_2$	yield: 3% ee: 4%	yield: 2% ee: 7%
$Pd(OAc)_2$ + (*S*)-MeO-MOP *o*-MeO-$C_6H_4B(OH)_2$	yield: 3% ee: 9.5%	yield: 2% ee: 8.5%
$Pd(OAc)_2$ + (*S*)-MeO-MOP *o*-MeCO-$C_6H_4B(OH)_2$	yield: 2% ee: 8%	yield: 2% ee: 8%

[a] All the reactions were carried out under nitrogen using CsF (3 eq), R = C_6H_4-*o*-OMe or C_6H_4-*o*-MeCO depending on the boronic acid employed.

The use of dimethylated substrate **173** in enantioselective Suzuki reactions provided the monosubstituted products in up to 13% ee. This enhancement in enantioselectivity (from 8 to 13%) shows that the presence of the bulky methyl groups in the vicinity of the oxidative addition step does have an effect on the enantioselectivity. However, when methyl substituents are present it is more difficult for the catalyst to approach the 1,1-dibromoalkene bond thus decreasing the yield of products formed.

Although various conditions for asymmetric reactions were attempted, the results were not as good as hoped. One of the main problems in the system studied is the reactivity of the starting materials. We anticipated than diiodide **192** would be more reactive; the preparation of **192** was attempted but was unfortunately unsuccessful (Scheme 32). There are no examples in the literature of the corresponding 1,1-ditriflates.



169 **192**

Scheme 32

Conclusions

The palladium catalysed Suzuki cross-coupling reactions of selected 1,1-dibromoalkene substrates provided mono and substituted products in low yields. It was possible to achieve the desymmetrisation of these dibromoolefin starting materials in Suzuki reactions with low enantioselectivities (up to 13% ee). Increased steric bulk has an

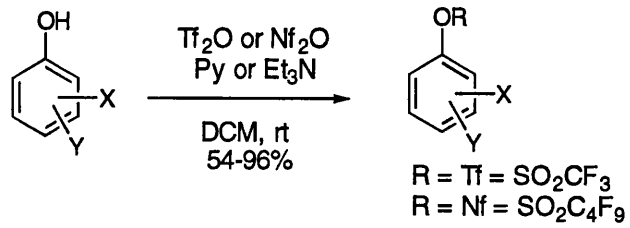
effect on the enantioselectivity, but the main limitation is the low reactivity of the dibromides. The design of alternative substrates based on cyclic 1,4-divinyltriflate skeletons which we speculated would be more active will be considered next.

Chapter 4: The preparation and use of cyclic 1,3-dione derived triflates in Suzuki cross-coupling reactions

Synthesis and uses of triflates in catalysed palladium couplings

Since vinyl trifluoromethane sulfonates (triflates) were first discovered simultaneously by Jones and Stang in 1969,[140] they have been widely used as synthetic precursors for vinyl cations and alkylidene substrates.[141,142] In the last decade the scope of the application of aryl and vinyl triflates has broadened enormously. One of the main reasons for this interest was the discovery of cross-coupling reactions of aryl and vinyl triflates with organometallic compounds. These reactions proceed with high regioselectivity under mild conditions and tolerate the presence of various functional groups.[143] Other derivatives from fluorosulfonic, nonafluorobutanesulfonic and other fluoro-containing sulfonic acids have also been found to react cleanly in cross-couplings with organometallic substrates, however these fluorosulfonate compounds have been less well studied than triflates.

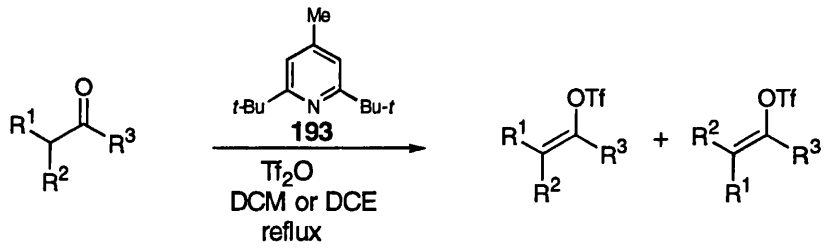
The synthesis of aryl or vinyl triflates can be achieved using several methods presented below. Aryl triflates and nonaflates are usually prepared in excellent yields from the phenol derivative which is treated with a weak base such as triethylamine or pyridine in combination with trifluoromethane sulfonic anhydride (triflic anhydride, Tf_2O) in DCM (Scheme 33).[144]



Scheme 33

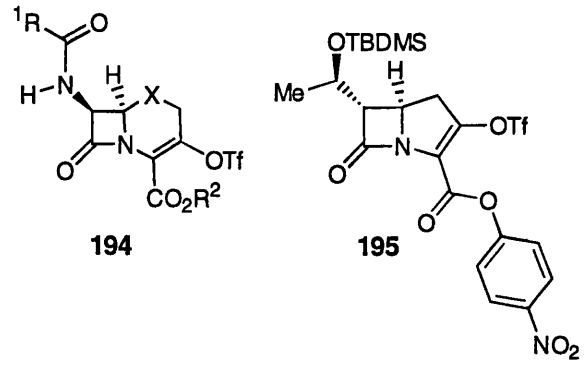
Aromatic *N*-heterocycles such as pyridines,[145,146] indoles[147] and quinolines,[148,149] bearing a hydroxy group are all converted to the corresponding triflates by these methods.

The first method employed to prepare vinyl triflates involved the treatment of the carbonyl compound directly with triflic anhydride in the presence of a non-nucleophilic base. The base of choice is the sterically hindered 2,6-di-*t*-butyl-4-methylpyridine **193** (in preference to the simpler pyridine or collidine bases) since this base acts solely as an acid scavenger, and does not react with Tf_2O itself (Scheme 34).[150]



Scheme 34

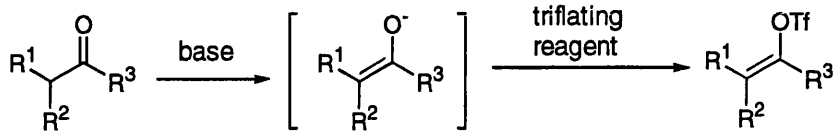
Mixtures of *E*- and *Z*-vinyl triflates are obtained for acyclic carbonyl compounds, the thermodynamically more stable *E*-vinyl triflate usually dominating. This method has been employed for the preparation of triflates **194** and **195** which are useful precursors for antibiotics (Figure 24).[151,152]



194 195

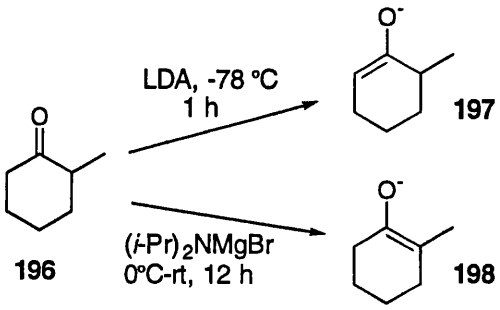
Figure 24

Vinyl triflates can also be prepared from the carbonyl compound by trapping the base-generated enolate with an electrophile source of triflate (Scheme 35). The enolate is generated with various strong bases such as LDA, $(i\text{-Pr})_2$NMgBr or NaHMDS.[153,154]



Scheme 35

The easier control of regio- and stereochemistry in cyclic systems led to the preference for the use of cycloalkenyl triflates in studies. Selective enolisation of α-substituted cyclohexanones such as 2-methylcyclohexanone **196** is achieved by imposing kinetic or thermodynamic control. Deprotonation at the less encumbered site by the bulky base lithium diisopropylamide gave the kinetic enolate **197** with a regioselectivity of 95:5, whereas the thermodynamic enolate **198** is obtained under equilibrium conditions by using bromomagnesium di*iso*propylamide.[153,155] Thus either regioisomeric compounds could be obtained in high yields and high selectivity (Scheme 36).



Scheme 36

N-Phenyltriflimide **199** first applied in 1983 has been very popular for the preparation of triflate compounds.[156] However its efficiency is not total in all cases; a disadvantage of using *N*-phenyltriflimide as the triflating agent is its low reactivity. Typically, reactions require several hours at 0 °C to efficiently trap a ketone metallo enolate. At this temperature some enolates are unstable or may equilibrate. Comins *et al* reported the successful use of two different pyridine derived triflating reagents, *N*-(2-pyridyl)triflimide **200** and *N*-(5-chloro-2-pyridyl)triflimide **201** in the synthesis of triflate substrates (Figure 25).[157] The triflating reagents **200** and **201** are more reactive than **199** in the reactions with enolates because the electron poor pyridine ring makes these triflating reagents very powerful electrophiles (compared to an aromatic ring such as **199**), thus they are more susceptible to nucleophilic attack.

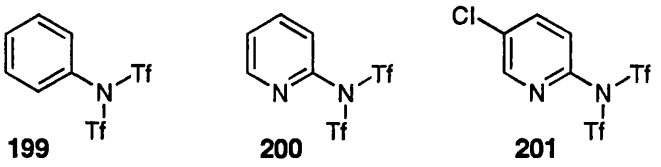
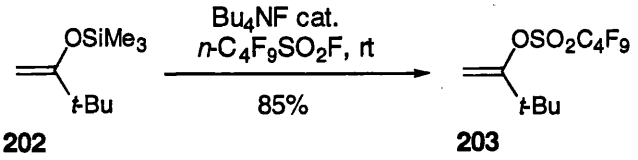


Figure 25

The *N*-pyridyltriflimides **200** and **201** are crystalline air stable compounds readily prepared on a large scale in one step from 2-aminopyridine, pyridine and triflic anhydride in DCM. The desired triflimide compounds **200** and **201** are then easily purified by distillation.

As a source of the nonaflate group the corresponding sulfonyl fluoride, an industrial product can be utilised.[143] As well as the corresponding synthesis from enolates,[158] vinyl nonaflates **203** may be obtained from silyl enol ethers **202** and nonafluorobutanesulfonyl fluoride in the presence of catalytic amounts of fluoride (Scheme 37).[159]

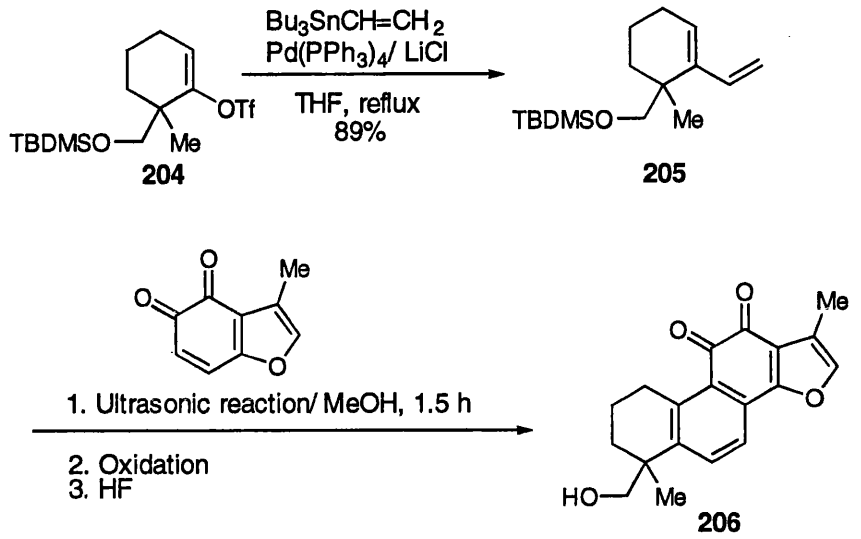


202 **203**

Scheme 37

Vinyl nonaflates may also be prepared by treatment of the ketone with nonafluorosulfonic anhydride.[160]

Due to the excellent leaving group properties of the triflate group, vinyl and aryl triflates have been widely used in palladium catalysed coupling reactions with organometallic compounds such as organotin, -zinc, -boron or -aluminium. Coupling reactions involving alkenes (Heck reaction), alkynes, the combination of an alcohol or amine (amination), with carbon monoxide (carbonylation) and allenes are also feasible. Numerous examples of coupling reactions with triflates and catalytic palladium are contained in the literature, including several employing a triflate in the key step of a natural product or drug synthesis.[161,162] For example, the Stille coupling reaction of cyclic vinyl triflate **204** with vinyltributyltin and tetrakis(triphenylphosphine)palladium provides diene **205** in excellent yield. Further functionalisation *via* a Diels-Alder reaction, oxidation and finally deprotection of the alcohol moiety delivers tanshinone IIB **206**, an ingredient of Chinese sage (Scheme 38).[163]

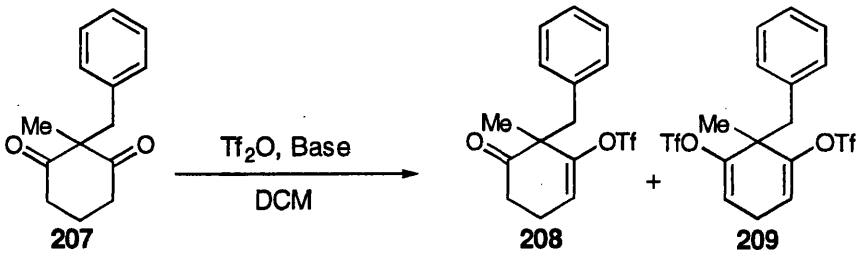


Scheme 38

Nonaflate compounds were also reported to successfully couple with organometallic substrates in palladium catalysed reactions. These fluorosulfonate compounds can be prepared from commercially available and cheap starting materials, hence they are attractive substrates for use in catalytic reactions. However, only a few examples of catalytic reactions involving nonaflates have been reported.

Preparation of mono and ditriflate substrates

The preparation of ditriflate **209** from diketone **207** was first investigated. The diketone **207** was prepared in 83% yield by alkylation of 2-methyl-1,3-cyclohexadione with benzylbromide following a literature procedure.[164] The diketone **207** was treated with triflic anhydride and various bases (Table 19).



207 208 209

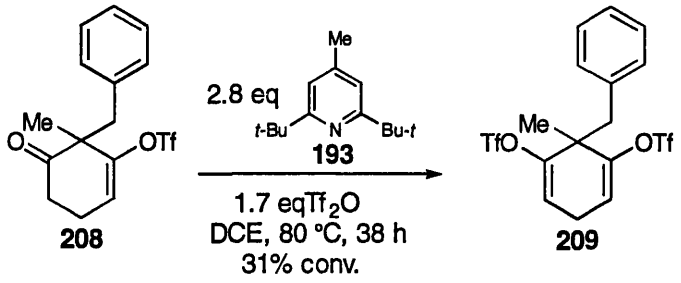
Table 19: Treatment of diketone **207** with triflic anhydride and various bases

Entry	Base	Tf_2O (eq)	Solvent, T°C	Yield [a] of **208** (%)	Yield [a] of **209** (%)
1	Na_2CO_3, 0.8 eq	4.0	DCM, rt	8	1
2	py, 1.1 eq	4.0	DCM, rt	20	0
3	collidine, 3.0 eq	3.0	DCE, 80	37	11
4	2,6-di-*t*-butyl 4-methylpy, 1.2 eq	1.1	DCE,80	44	0
5	2,6-di-*t*-butyl 4-methylpy, 2.2 eq	2.1	DCE, 80	73	5

[a] Isolated yields after purification by flash column chromatography.

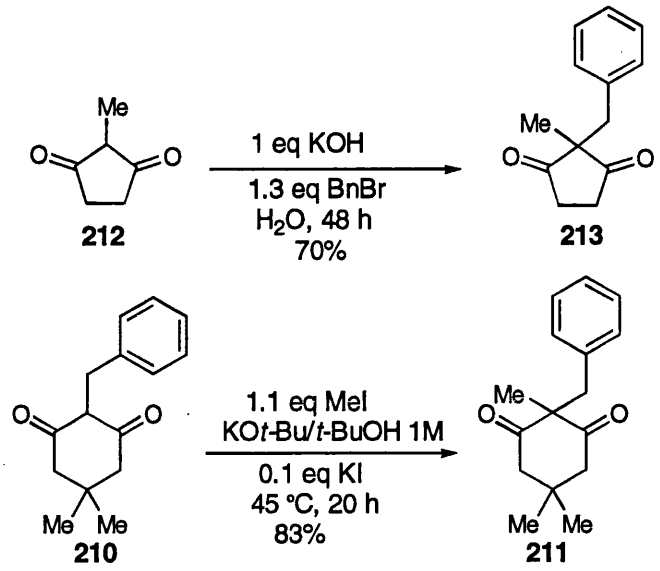
In all the experiments performed, the reactions were complete within one day at room temperature or reflux, providing by tlc the two possible products, monotriflate **208** and ditriflate **209** in various ratios. Unfortunately the desired ditriflate **209** was always formed in low yields. The aqueous work-up seemed to be problematic, especially when the base Na_2CO_3 (Entry 1) was used. It was found that the sterically hindered base 2,6-di-*t*-butyl-4-methylpyridine **193** enables the formation of the monotriflate **208** in good yield (73%) along with a small amount of ditriflate **209**. In this case the work-up consists of filtration of the by-product pyridinium salt formed during the reaction followed by concentration of the remaining filtrate under reduced pressure. The reaction carried out with an excess of both triflating reagent and 2,6-di-*t*-butyl-4-methylpyridine **193** (4 eq) in refluxing DCE afforded only a mixture of monotriflate **208** and ditriflate **209** in 31% and 43% yield respectively. The conversion of monotriflate **208** to ditriflate **209** employing the hindered pyridine base (2.8 eq) and triflic anhydride

(1.7 eq) in refluxing DCE at reflux for 38 h was similarly unsuccessful (Scheme 39). One pleasing quality of these two triflates is their relatively good stability toward purification by flash column chromatography. These compounds are stable towards storage in the refridgerator for long periods of time.



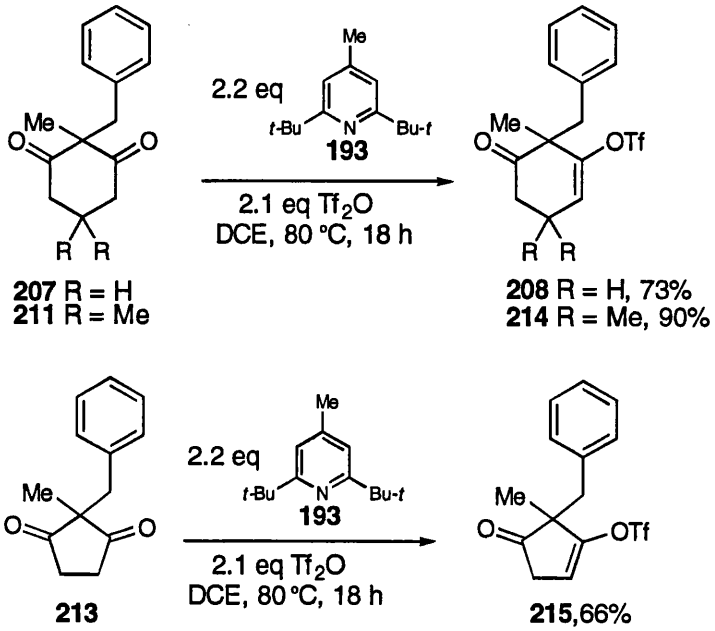
Scheme 39

Two further cyclic diketones **211** and **213** were prepared *via* alkylation with benzylbromide or iodomethane (Scheme 40). 2-Benzyl-2-methyl-cyclopentadione **213** was obtained by treatment of commercially available 2-methyl-cyclopentadione **212** with benzylbromide in 75% yield.[164] Furthermore, 2-benzyl-2,5,5-trimethyl-cyclohexadione **211** was synthesised by methylation of 2-benzyl-5,5-dimethyl-cyclohexadione[165] **210** in 83 % yield.[166]



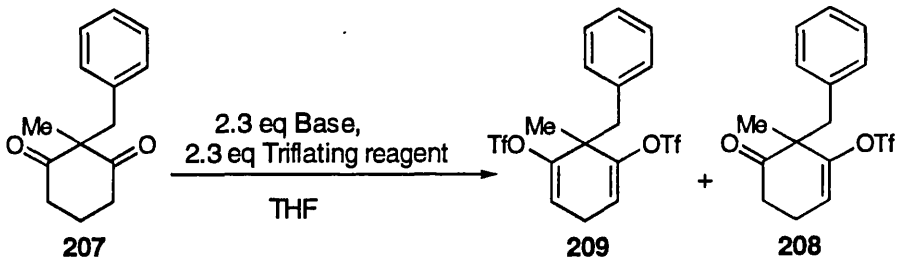
Scheme 40

When dialkylated diketones **211** and **213** were treated with triflic anhydride (2.1 eq) and 2,6-di-*t*-butyl-4-methylpyridine **193** (2.2 eq) in DCE at reflux for one day, the monotriflates **214** and **215** were formed as the major products (Scheme 41). This represents a general method for the preparation of monotriflate compounds from cyclic 1,3-diketones.



Scheme 41

The formation of ditriflate **209** through the formation of the respective enolate was next investigated. Two strong bases, lithium diisopropylamide and potassium hexamethyldisilazide, were employed in the reaction. *N*-phenyltriflimide **199** and *N*-(5-chloro-2-pyridyl)triflimide **201** were the two triflating reagents used. Two different methods have been employed; one method (method a) consists of adding the base to the ketone in THF at -78 °C and stirring for one hour before addition of the triflating reagent. Whereas, the other method (method b) is the inverse addition of the base to a mixture of ketone and triflating compound in THF at -78 °C, and then stirring the solution for one hour (Table 20).



207 **209** **208**

Method a: base added to the ketone and then triflimide added to the resulting enolate at -78°C
Method b: base added to a mixture of triflimide and ketone at -78 °C

Table 20: Treatment of diketone **207** with triflating reagents **199** or **201**

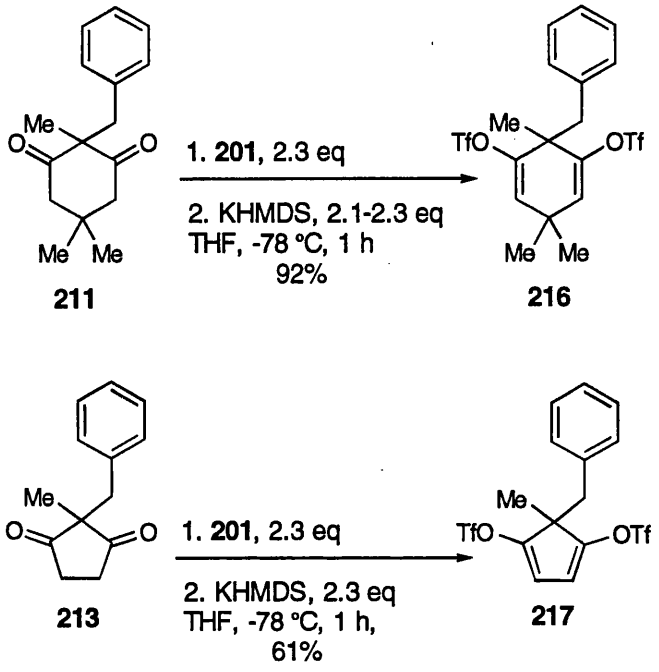
Entry	Method	Base	Triflating reagent	recovered **207** (%)	Yield of **208** (%)	Yield of **209** (%)
1	a	LDA	**192**	14	36	25
2	a	KHMDS	**194**	25	33	22
3	b	KHMDS	**194**	28	15	41
4	a*	KHMDS	**194**	10	13	55

* 1.2 eq of base added to the ketone, followed by 1.2 eq of triflimide, 1.2 eq of base and then finally 1.2 eq of triflimide added to the mixture, all at -78 °C.

The use of method a to prepare the diketone **209** was not very successful since the expected product was formed in moderate yields (Entries 1 and 2) when phenyltriflimide **199** and *N*-(5-chloro-2-pyridyl)triflimide **201** were employed in the reaction. The major product formed was the monotriflate **208** obtained ca 35% yield. It

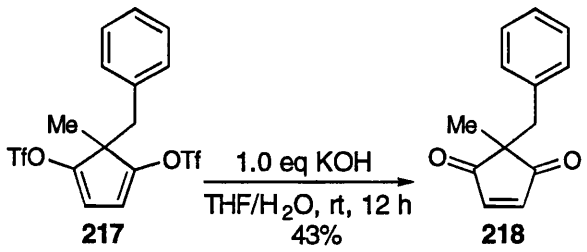
was found that the solution became increasingly viscous after the addition of the base (2.3 eq) to the ketone at -78 °C, thus making the stirring impossible and presumably the access of the triflimide to the anion very difficult. Addition of the base and the triflimide in two equal portions to the ketone provided the formation of the ditriflate **209** in up to 55% yield along with 13% of monotriflate **208** (Entry 4). It was hoped that the treatment of diketone **207** with 1.2 eq of base and then 1.2 eq of triflimide **201** would exclusively afford monotriflate **208**, however a tlc of the reaction indicated the formation of monotriflate **208** as a major product along with a small amount of ditriflate **209** and starting material **207**. The strong bases LDA and KHMDS employed may react with the acidic proton (allylic protons) of the ditriflate **209** already formed thus explaining the rather moderate yields of ditriflate **209** obtained. The inverse addition of the base (2.3 eq) to a solution of the diketone and the triflimide (2.3 eq) in THF did not result in any improvement of the yield of ditriflate **209** (Entry 3).

Dimethylated diketone **211** and cyclopentadione **213** were also treated with 5-chloro-pyridinetriflimide **201** and KHMDS at -78 °C for 1 h. The ditriflates **216** and **217** were formed in 61% and 92% yield respectively (Scheme 42). The order of addition of the reagents is very important in the preparation of ditriflate **217**. Thus, the treatment of 1,3-cyclopentadione **213** with the strong base KHMDS for one hour followed by addition of the triflimide reagent led to a dark red solution, tlc analysis showed very little of the expected product along with decomposed product(s) (major spot on the base line on the tlc). The inverse addition (base added to a stirred mixture of ketone and triflimide compound) was then preferred for the synthesis of ditriflate **217**. This method was found to also be efficient for the preparation of dimethylated ditriflate **216**.



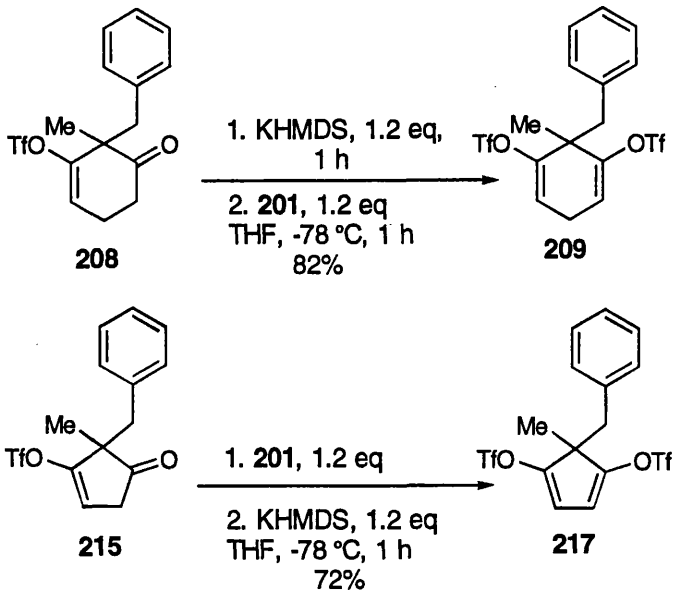
Scheme 42

The reaction of 1,3-cyclopendione **213** with 5-chloro-pyridinetriflimide and KHMDS provides the ditriflate **217** in good yield (61%), however it is affected by the formation of a side product which was shown to be diketone **218** (yields range between 10 and 15%). This product **218** is also observed when ditriflate **217** and monotriflate **215** are treated with aqueous base (KOH) in THF (Scheme 43). The use of exactly 2.0 eq of base did not help to reduce the formation of this side product **218.**



Scheme 43

When monotriflates **208** and **215** were reacted with KHMDS (1.1 eq) and 5-chloro-pyridinetriflimide, the ditriflates **209** and **217** were formed in 82% and 72% yield respectively (Scheme 44).



Scheme 44

The three monotriflate compounds **208, 214** and **215** are racemic compounds possessing a quaternary carbon and could be subjected to kinetic resolution *via* a cross-coupling reaction using a chiral palladium catalyst. The three ditriflate substrates **209, 216** and **217** which are symmetrical compounds can be subjected to enantioselective desymmetrisation *via* palladium catalysed reactions.

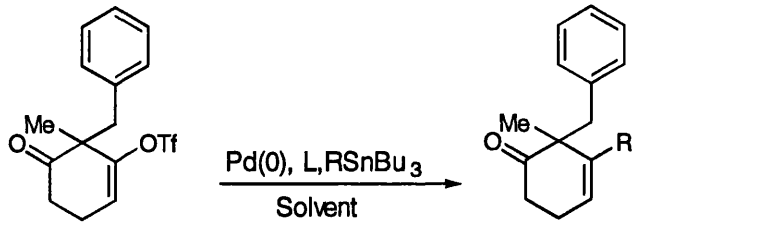
Palladium coupling reactions of mono and ditriflates with achiral catalysts

The reactivity of each of the six triflate compounds was first studied in palladium catalysed reactions with organotin or organoboron compounds using simple achiral catalysts. The reactions were performed with catalysts prepared from $Pd(dba)_2$ or $Pd(OAc)_2$. The results obtained provided a useful guide for the asymmetric couplings of these same substrates.

Reactivity of monotriflates

The reactivity of triflate **208** was first studied in two different palladium catalysed reactions with achiral catalysts: Stille and Suzuki cross-couplings.

The Stille couplings were carried out using either tributylphenyltin or tributylvinyltin, in THF or NMP at room temperature or at 35 °C. The catalyst employed was prepared *in situ* from $Pd(dba)_2$ and either tri-(furyl)phosphine or triphenylarsine (Table 21).



208

219, R = -CH=CH$_2$
220, R = Ph

Table 21: Stille coupling employing triflate **208** [a]

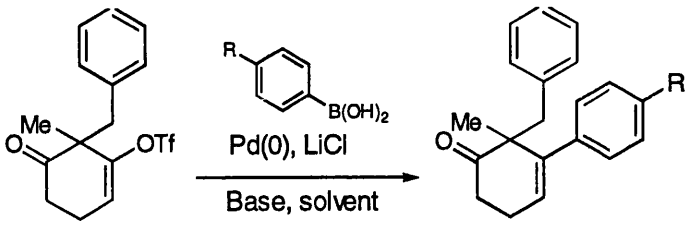
Entry	Bu_3SnR	L	Solvent, T ºC	Time (days)	Yield of product (conv.) [b]
1	$Bu_3Sn(CH=CH_2)$	TFP	THF, rt	4	67%, (100%)
2	$Bu_3Sn(CH=CH_2)$	TFP	NMP, rt	2	(100%)
3	$Bu_3Sn(CH=CH_2)$	TFP	NMP, 35	1	65%, (100%)
4	Bu_3SnPh	$AsPh_3$	NMP, 35	1	87%, (100%)

[a] Reactions were carried out with 10 mol% of Pd(dba)2, 20 mol% of ligand L, 3.0 eq of LiCl and 1.25 eq of tin reagent.[b] Isolated yield after purification by flash column chromatography (conversion was determined by ^{1}H NMR)

The reactions performed were all complete within one to four days and the isolated yields of the desired coupling product **219** and **220** were good (65-87%). It was interesting to note that the reaction carried out in THF (Entry 1) required more time to go to completion compared to the analogous reaction performed in NMP (Entry 2).

The reactivity of monotriflate **208** was also investigated in Suzuki coupling reactions employing four different boronic acids; phenylboronic acid **125**, 4-methoxyphenylboronic acid **180**, 4-acetylphenylboronic acid **181** and 4-*t*-butylphenylboronic acid **221**. The reactions were performed in either THF or dioxane at

either room temperature or at reflux. The catalysts employed were either tetrakis(triphenylphosphine)palladium or a mixture of $Pd(dba)_2$ or $Pd(OAc)_2$ and triphenylphosphine. The results of the Suzuki couplings with **208** are listed in Table 22.



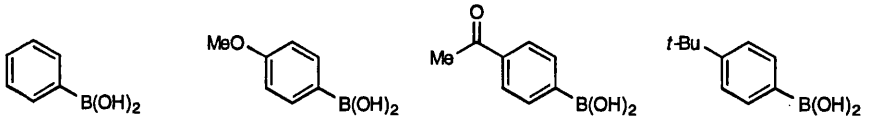
208

220, R = H
222, R = MeO
223, R = CH_3CO
224, R = *t*-Bu

Table 22: Suzuki coupling reactions of triflate **208** with various boronic acid [a]

Boronic acid	Entry	Catalyst	Solvent, T°C	Time (h)	LiCl (eq)	Base	recovered **208**	Yield[b] of **product** (conv.)
125	1	$Pd(PPh_3)_4$	dioxane, 60	12	3	Cs_2CO_3	0%	58%
	2	$Pd(PPh_3)_4$	THF/H_2O, rt	70	3	KOH	27%	69%
	3	$Pd(PPh_3)_4$	THF/H_2O, rt	12	3	TlOH	19%	64%
180	4	$Pd(OAc)_2/PPh_3$	THF/H_2O, rt	48	3	KOH	nd	77%
	5	**$Pd(OAc)_2/PPh_3$**	**THF/H_2O, rt**	**0.75**	**-**	**KOH**	**nd**	**82%**
	6	$Pd(PPh_3)_4$	dioxane, 65	24	-	K_3PO_4	nd	(66%)
	7	$Pd(PPh_3)_4$	dioxane, 65	24	3	K_3PO_4	nd	(55%)
	8	$Pd(OAc)_2/PPh_3$	dioxane, rt	1	-	CsF	nd	(100%)
181	9	$Pd(OAc)_2/PPh_3$	THF/H_2O, rt	70	3	KOH	nd	0%
	10	$Pd(OAc)_2/PPh_3$	THF/H_2O, rt	2.5	-	KOH	nd	78%
	11	$Pd(PPh_3)_4$	THF/H_2O, rt	72	3	TlOH	nd	74%
221	12	$Pd(PPh_3)_4$	THF/H_2O, rt	70	3	KOH	nd	47%
	13	$Pd(dba)_2/PPh_3$	THF/H_2O, rt	70	3	TlOH	57%	19%
	14	$Pd(OAc)_2$	THF/H_2O, rt	2.5	-	KOH	nd	58%

[a] Reactions were carried out with 1.25 eq of phenylboronic acid, 10 mol% Pd(0), 20 mol% triphenylphosphine, 1.0 eq of KOH or TlOH or 3.0 eq of CsF. [b] Isolated yield after purification by flash column chromatography (conversion was determined by ^1H NMR).



125 **180** **181** **221**

The coupling reactions of monotriflate **208** with the four different arylboronic acids provided the coupled product in low to good yields (19%-82%). The exception was the reaction of 4-acetylphenylboronic acid **181** in the presence of additive lithium chloride, where no reaction occurred (Entry 9). The results demonstrate that various inorganic bases (Cs_2CO_3, CsF, K_3PO_4, KOH, TlOH) can be employed to successfully carry out the Suzuki couplings. The palladium catalyst prepared from $Pd(dba)_2$ and PPh_3 was found to be less active than those catalysts prepared from $Pd(OAc)_2$ and PPh_3 (Entries 4 and 13). It has been reported that the use of lithium chloride is usually required in palladium couplings employing triflates to avoid premature precipitation of the catalyst, especially when tetrakis(triphenylphosphine)palladium (0) is employed as the palladium source (Figure 24).

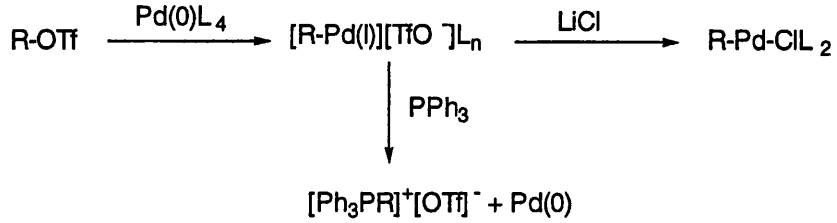
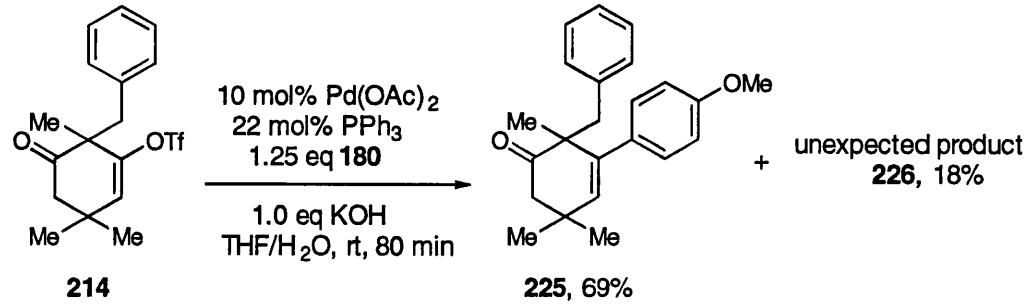


Figure 24

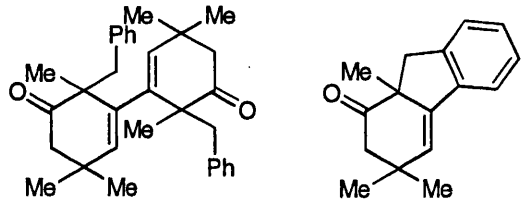
In our system it was apparent that the use of lithium chloride was slowing down the reaction rate of the coupling reactions; the reaction of triflate **208** with 4-methoxyphenylboronic acid **180** and lithium chloride was not complete after 48 h (tlc showed some starting material unreacted). However, the same coupling reaction when carried out in the absence of lithium chloride was complete in only 40 minutes (Entries 4 and 5).

The dimethylated monotriflate **214** and five membered ring monotriflate **215** were subject to Suzuki cross-coupling reaction with 4-methoxyphenylboronic acid **180**. The optimum conditions identified for the coupling of monotriflate **208** ($Pd(OAc)_2/PPh_3$, THF/H_2O at room temperature with KOH and no lithium chloride) were first applied (Entry 5). The Suzuki cross-coupling of dimethylated monotriflate **214** was complete in 80 minutes (the reaction requires 40 min when no methyl groups are present in the molecule) at room temperature. This showed that the presence of methyl substituents slows down the reaction rate. Two products were isolated after purification by flash chromatography (Scheme 45); the expected coupled product **225** in 69% yield along with a second product **226** in 8% yield. Compound **226** possesses a ^1H NMR similar to the ^1H NMR of the starting material **214** except that the chemical shifts are slightly different. The IR spectra and the ^{13}C NMR of **226** did not show the presence of a triflate group and only a carbonyl group was observed.



Scheme 45

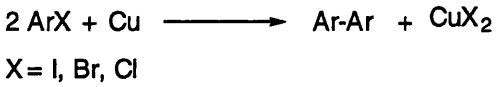
Product **226** could arise from either the coupling of two molecules of triflate **214** (compound **226a**) under palladium catalysed conditions or from an intramolecular coupling between the triflate group and the benzene ring (compound **226b**) as presented in Figure 26.



226a 226b

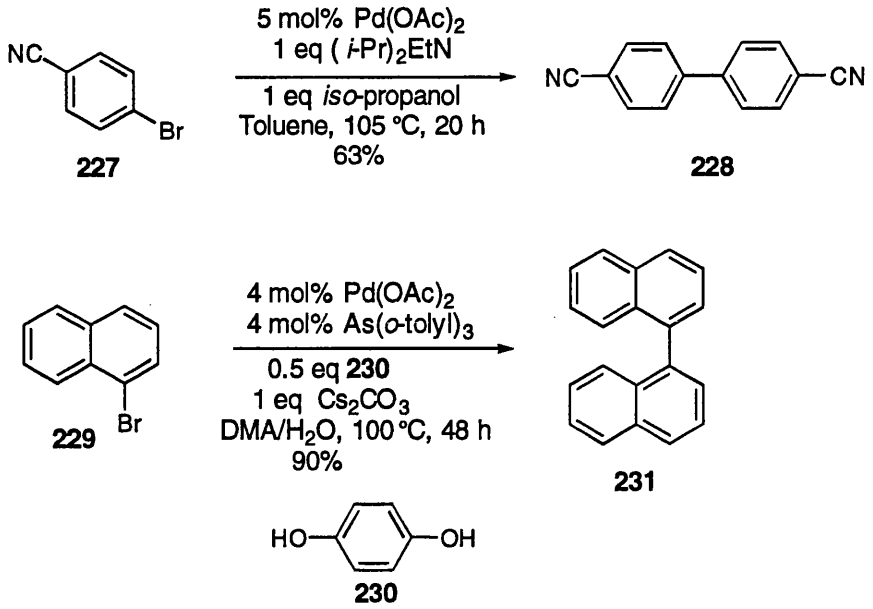
Figure 26

The homocoupling reaction of halide or triflate aryls catalysed by metals has been reported in the past. The Ullman coupling, which involves the coupling of two molecules of aryl halide with stoichiometric amount of cupper, is well documented (Scheme 46).[167]



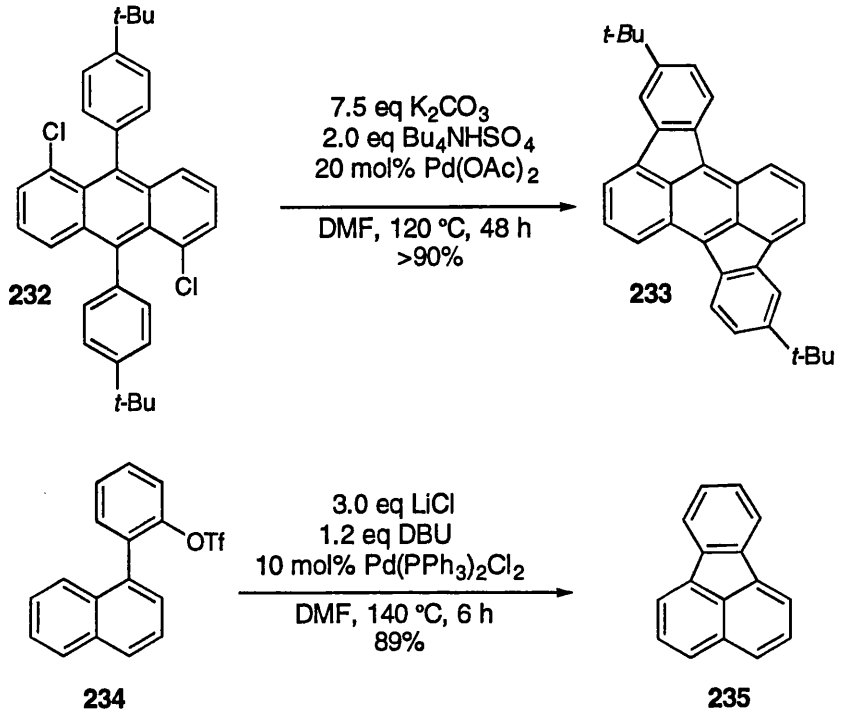
Scheme 46

The homocoupling of arylhalides catalysed by palladium species is less well known and most of the couplings require the use of an additive which enables the reduction of the palladium species *in situ* to regenerate the active catalyst (Scheme 46). The reductive agents can be a proton-transfer agent (*e.g.* methanol or hydroquinone), hydrogen gas or phosphines (triarylphosphines).[168-170] For example the self coupling of 4-bromobenzonitrile **227** in the presence of di-*iso*-propylamine and *iso*-propanol (as the reducing agent) catalysed by $Pd(OAc)_2$ in toluene at reflux provides the biaryl compound **228** in 63% yield (Scheme 47).[171] This method has then been utilised to prepare achiral 1,1'-binaphthyl compounds which when substituted in the 2,2' position are good candidates for the formation of atropoisomers. Thus, the homocoupling of 1-bromonaphthalene **229** employing 0.5 eq of the reducing agent hydroquinone **230** and 1.0 eq of Cs_2CO_3 catalysed by a mixture of $Pd(OAc)_2$ and As(*o*-tolyl)$_3$ afforded the 1,1'-binaphtyl product **231** in 90% yield (Scheme 47).[172]



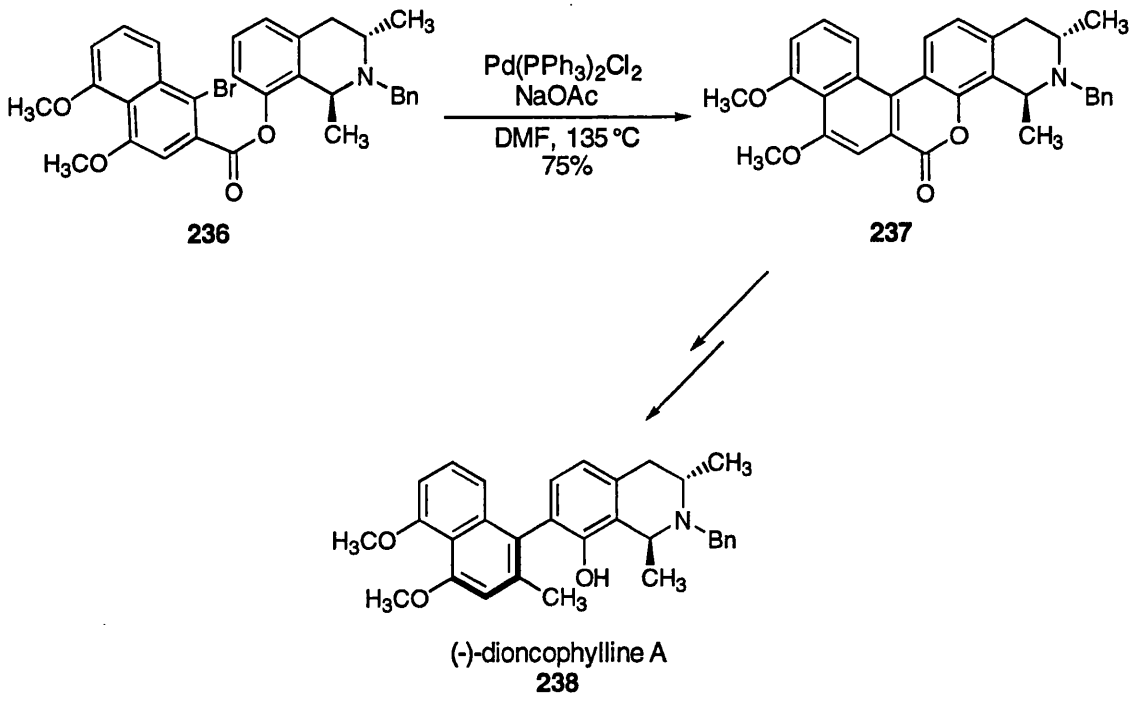
Scheme 47

Examples of palladium catalysed intramolecular arylation reactions have also been reported in the literature. This type of coupling has been specifically used to prepare polyheterocycle compounds such as fluoranthenes, benzofluoroanthenes,[173,174] dibenzofuran,[175] carbazoles and fluorenones.[176] The reaction usually requires forcing reaction conditions with high temperatures (120 to 170 °C). For example, the intramolecular arylation of diarylanthracene **232** in the presence of $Pd(OAc)_2$, Bu_4NHSO_4, the base K_2CO_3 in DMF at 120°C for 2 days delivered the desired rubicene **233** in excellent yield (>90%) (Scheme 48).[177] Fluoranthene **235** was prepared in good yield (89%) *via* the intramolecular coupling of substituted naphthalene **234** in the presence of $Pd(PPh_3)_2Cl_2$, LiCl and DBU in DMF at 140 °C for 6 h (Scheme 48).[178]



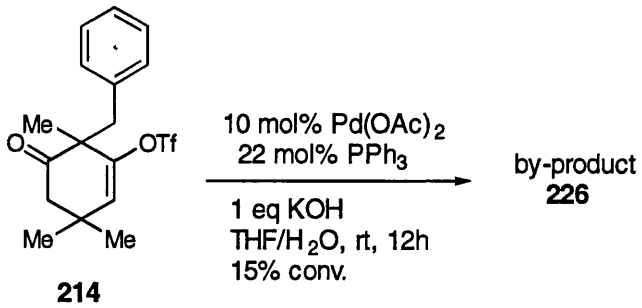
Scheme 48

The palladium catalysed intramolecular arylation has also been used as a key step for the synthesis of several natural products.[179,180] For example, (-)-dioncophylline A **238** which belongs to a new group of naphthylisoquinoline alkaloids, was synthesised employing an intramolecular coupling reaction as the key step. Thus, substituted naphthalene **236** was subject to an intramolecular coupling employing $Pd(PPh_3)_2Cl_2$, NaOAc in DMA at 130 °C to afford the lactone **237** in 75% yield.[181] A further functionalisation afforded the desired dioncophylline A **238** (Scheme 49).



Scheme 49

When monotriflate **214** is reacted with palladium catalyst ($Pd(OAc)_2/PPh_3$) in the presence of 1.0 eq of base in THF for 12 h at room temperature, the formation of the by-product **226** is observed. The conversion of the starting material is however low (15% conv.) and towards the end of the reaction the precipitation of palladium black was observed (Scheme 50).

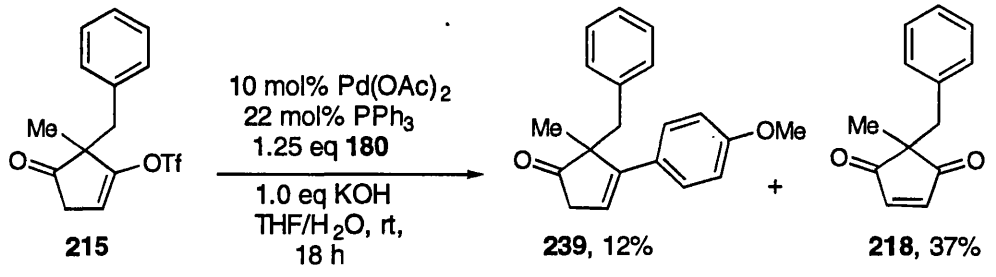


Scheme 50

The mass spectra of the unknown product revealed a molecular ion peak of 226 which corresponds to the product **226b** and confirms its formation from the intramolecular

reaction of the starting material. This intramolecular homocoupling of a vinyl triflate with an aromatic ring is very unusual and to the best of our knowledge no examples have been reported in the literature. Moreover the conditions required for this coupling are much milder than any of the conditions usually employed for the intramolecular aryltriflate arylations.

The Suzuki coupling reaction of monotriflate **215** was also investigated; treatment of triflate **215** with 4-methoxyphenylboronic acid **180** (Scheme 51) after 18 h afforded the desired coupled product **239** in a disappointing 12% yield, along with 37% of side-product **218** and a small amount of recovered starting material **215** (9%). The poor reactivity may be due to the presence of acidic allylic protons which can react under the basic conditions necessary for Suzuki couplings.

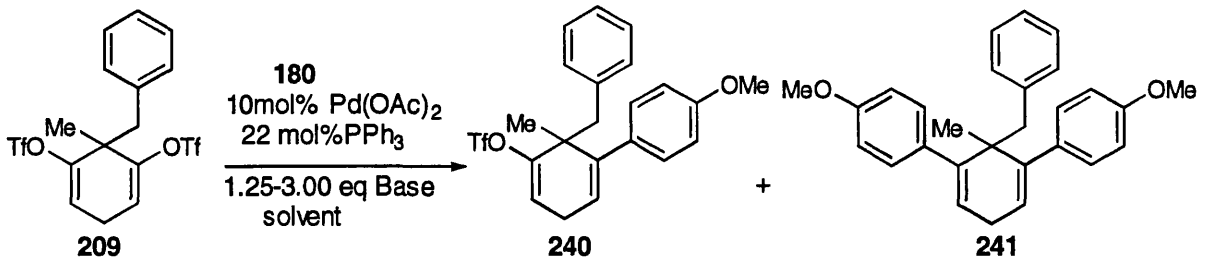


215 **239**, 12% **218**, 37%

Scheme 51

Reactivity of ditriflates

The reactivities of ditriflates **209, 216** and **217** were also evaluated in Suzuki coupling reactions with achiral catalysts. The six membered ring ditriflate **209** was first studied in palladium catalysed couplings with 4-methoxyphenylboronic acid **180.** Selected conditions for the coupling reactions are shown in Table 23.



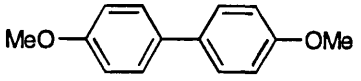
209 240 241

Table 23: Suzuki cross coupling of ditriflate **209** with 4-methoxyphenylboronic acid **180** [a]

Entry	**180** eq of	Base	solvent, T °C	h	recovered **209** (%)	Yield of **240**[b] (%)	Yield of **241**[b] (%)
1	1.25	KOH	THF/H_2O, rt	14	44	4	0
2	1.25	KOH	THF/H_2O, rt	18	19	7	8
3	1.25	Na_2CO_3	THF/H_2O, rt	20	45	6	6
4	1.25	K_3PO_4	dioxane, 70	12	nd	<5	<5
5	1.25	CsF	dioxane, rt	15	22	0	0
6	4.00	CsF	dioxane, rt	15	2	0	21[c]

[a] Reactions were carried out with 1.25 eq of KOH, Na2CO3 ,1.5 eq of K3PO4 or 3 eq CsF.
[b] Isolated yields after purification by flash column chromatography. [c] Reaction was carried out with 6 eq of CsF.

The coupling reactions of ditriflate **209** with substituted phenylboronic acid **180** were not as successful as for the equivalent monotriflate **208.** In these cases, a significant amount of starting material was recovered (19-45%) and large quantities of by-product **242** (from the self coupling reaction of two molecules of boronic acid under palladium catalysed conditions[182]) were isolated after purification by flash chromatography (yields between 11 and 39%).

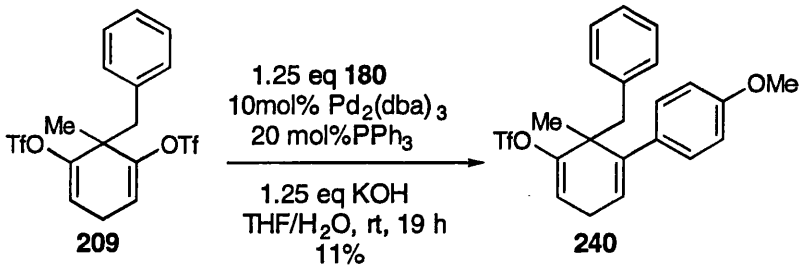


242

We attribute the poor reactivity of the ditriflate to the presence of acidic allylic protons in the starting material which can react with the strong inorganic base KOH. The two products **240** and **241** are however less likely to undergo deprotonation; an aromatic group substituted with a electron donating group (compared to a triflate group) makes the allylic protons less acidic. This possible deprotonation of the ditriflate **209** may

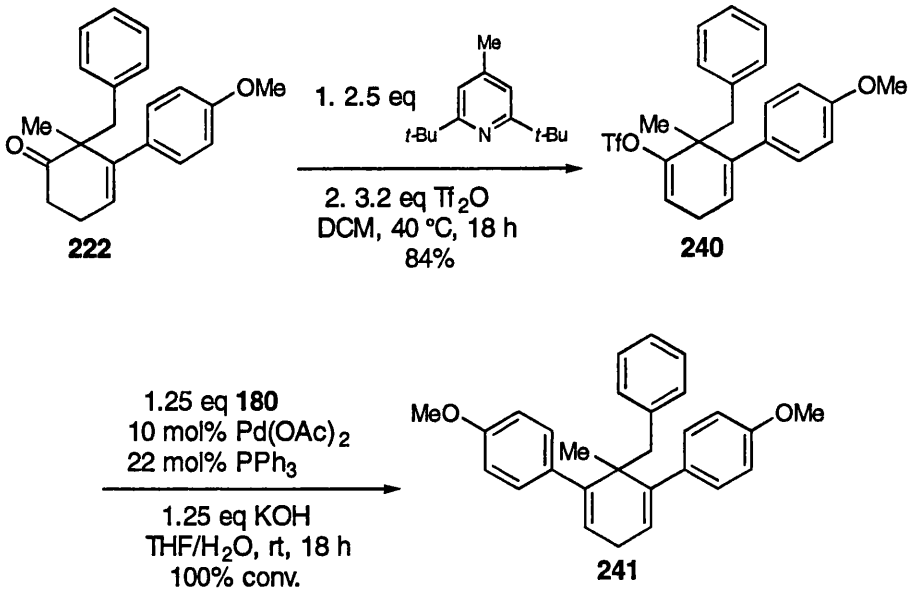
explain the loss of material (the total of recovered material **209**, monocoupled product **240** and dicoupled product **241** was always far below 100%). Alternative conditions have been investigated, for example, the use of weaker bases (Na_2CO_3, CsF, Et_3N) or slow addition of the base, but any improvement was not evident.

The use of $Pd_2(dba)_3$ as an alternative source of palladium in the Suzuki cross-coupling reactions of **209** with 4-methoxyphenylboronic acid provided the monocoupled product **241** in low yield (Scheme 52).



Scheme 52

The reactivity of monocoupled product **240** was also investigated under the standard conditions (10 mol% $Pd(OAc)_2$, 22 mol% PPh_3, 1.25 eq arylboronic acid **180** and 1.25 eq of KOH in THF/H_2O). Monotriflate **240** was prepared in 84% yield from the ketone **222** employing the hindered base 2,6-di-*t*-butyl-4-methylpyridine **193** and triflic anhydride in DCM (Scheme 53). The Suzuki reaction of monotriflate **240** was complete in 18 h and the formation of the dicoupled product **241** was observed by ^1H NMR.

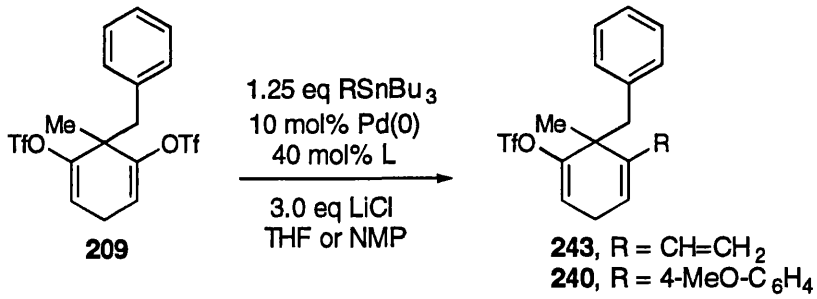


Scheme 53

This additional result shows that the monocoupled product **240** is very reactive towards Suzuki conditions used, and thus may explain why such small amounts of **240** are isolated when ditriflate **209** is treated with 4-methoxyphenylboronic acid **180.**

The strongly basic conditions employed in Suzuki coupling appears to limit the use of ditriflate **209.** Attention was therefore turned to Stille couplings and carbonylation reactions which do not require the use of any strong base.

The coupling reactions of substrate **209** with tributylvinyltin and (4-methoxyphenyl)tributyltin[183] were investigated employing various palladium catalysts ($Pd(PPh_3)_4$, $Pd(OAc)_2$+TFP, $Pd(OAc)_2$+$AsPh_3$) in either NMP or THF (Table 24).



209

243, R = $CH{=}CH_2$
240, R = 4-MeO-C_6H_4

Table 24: Stille coupling of ditriflate **209** with tributylvinyl tin or 4-methoxyphenyltributyl tin

	Entry	Pd catalyst	Solvent, T °C	Time (h)	recovered **209** (%)	Yield of product (%)
Bu_3Sn	1	$Pd_2(dba)_3$/TFP	THF, rt	22	85	trace
	2	$Pd_2(dba)_3$/TFP	THF, reflux	12	100	-
	3	$Pd(PPh_3)_4$	THF, reflux	8	17	35
MeO, $SnBu_3$	4	$Pd_2(dba)_3$/TFP	NMP, rt	24	100	-
	5	$Pd_2(dba)_3$/$AsPPh_3$	NMP, 50	24	100	-
	6	$Pd_2(dba)_3$/$AsPPh_3$	THF, reflux	24	100	-
	7	$Pd(PPh_3)_4$	THF, reflux	8	100	-

The Stille couplings of ditriflate **209** with substituted aryltributyltin compound were not successful at all with the starting material being recovered quantitatively in nearly all cases. The low reactivity of ditriflate **209** in Stille coupling reactions with substituted arylstannanes is not surprising since it has been reported earlier that aryl tin compounds are poorer nucleophiles than their vinyl tin counterparts for Stille cross-coupling reactions.[153] Pleasingly, the Stille coupling of ditriflate **209** with vinyl tributyltin catalysed by $Pd(PPh_3)_4$ in THF at reflux (Entry 3) afforded the monocoupled product in 35% yield along with some recovered starting material (17%) and a small amount of dicoupled product. However, in most cases the formation of homocoupled tin compound could be observed which shows the modest reactivity of ditriflate **209** in Stille coupling reactions. The Stille coupling reaction of **209** with vinyltributyltin employing Farina's conditions ($Pd_2(dba)_3$ + TFP) did not provide the expected coupled product **243** (Entry 1).

The ditriflate **209** was finally employed in a methoxycarbonylation catalysed by a palladium catalyst prepared *in situ* from palladium diacetate and triphenylphosphine. The catalytic cycle of a carbonylation process does not involve a transmetallation step; it consists of an oxidative addition of the halide to the palladium (0) followed by coordination and facile migratory insertion of carbon monoxide to provide the acyl palladium species. Final nucleophilic attack of an alcohol, water or an amine affords the resulting ester, carboxylic acid or amide (Figure 27).[184,185,186]

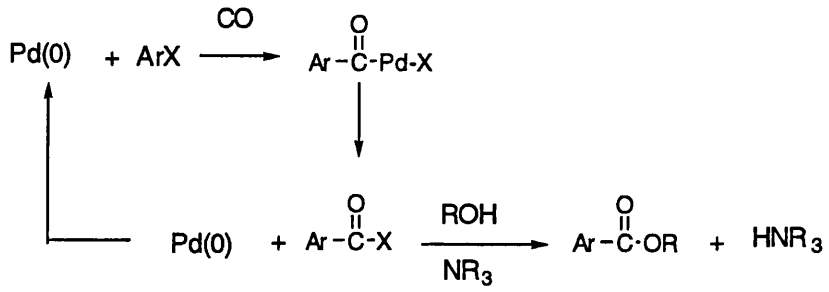
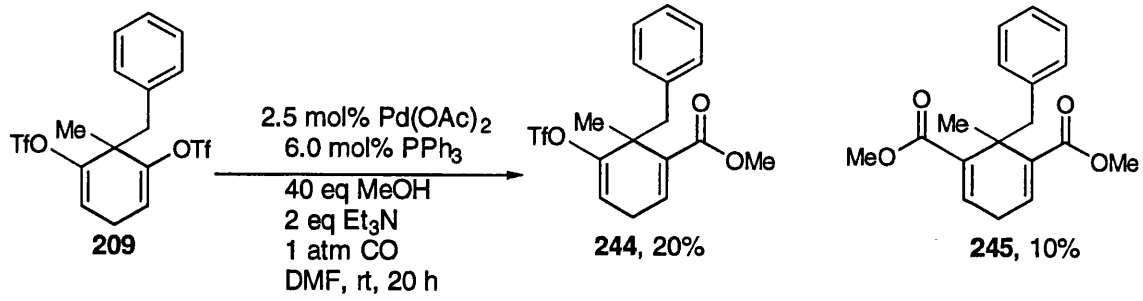


Figure 27

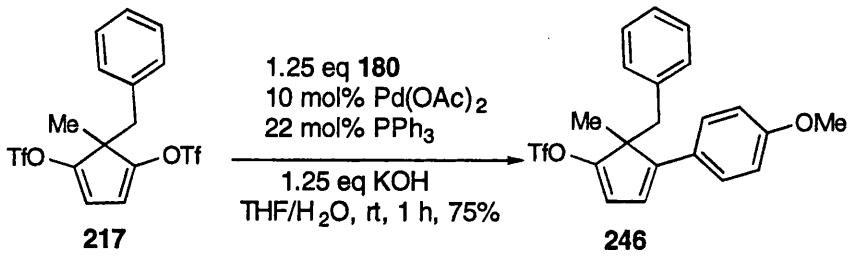
It was hoped that this feature of the carbonylation reaction would enhance the reactivity of ditriflate **209** in palladium catalysed reactions. The methoxycarbonylation of ditriflate **209** was carried out employing methanol as the nucleophile with $Pd(OAc)_2/PPh_3$ and triethylamine in DMF under 1 atm of carbon monoxide at room temperature for 20 h (Scheme 54).[187]



Scheme 54

The methoxycarbonylation pleasingly delivers the monoester **244** and the diester **245** in low yields (20 and 10% yield respectively) along with 59% of recovered starting material. This reaction has not been optimised, but the yields should be improved just by performing the reaction at higher temperatures (60-100 °C). This result shows that ditriflate **209** can be successfully used as a potential substrate for palladium catalysed cross-coupling reactions where the use of a strong base is not required.

The reactivity of cyclic five membered ring ditriflate **217** was also studied in Suzuki cross-coupling reactions. The substrate was reacted with 4-methoxyphenylboronic acid **180**, $Pd(OAc)_2$ and triphenylphosphine in THF at room temperature (Scheme 55). Surprisingly, the reaction was complete in one hour with exclusive formation of the monocoupled product **246** which was isolated as a solid in 75% yield after purification by flash chromatography. This high reactivity of ditriflate **217** is attributed to the conjugation of the two double bonds, a feature which was not present in the ditriflate **209**.

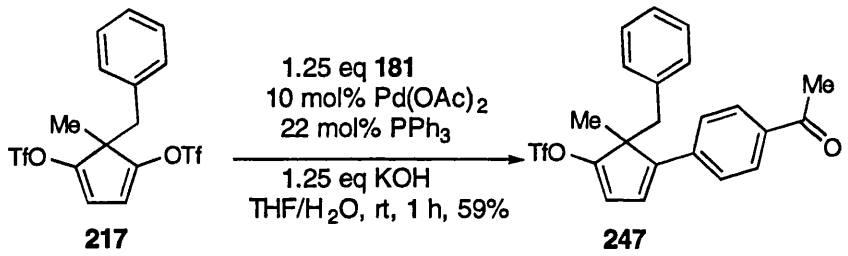


217 **246**

Scheme 55

Monocoupled product **246** is very unstable and decomposes rapidly upon exposure to air or in solution. This high reactivity of the coupled product which still possesses a triflate group may be attributed to the diene-aryl ring conjugation. Loss in isolated yields were noticed when purification was not performed immediately after the end of the reaction. For example, a 50% yield of coupled product **246** was isolated after

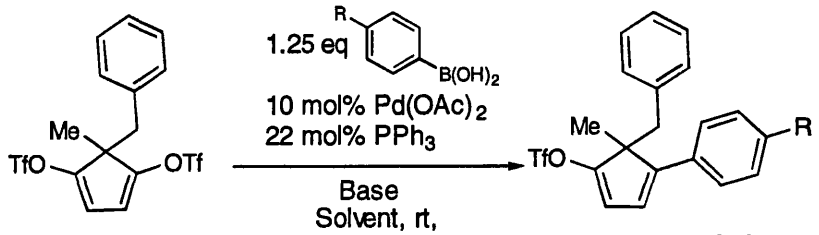
purification of a crude mixture (complete reaction) performed 3 days later. Reproducibility was also a problem and the yields (employing the same conditions) varied in the range 31-75%. The use of an electron withdrawing group on the phenylboronic acid in Suzuki coupling reaction with ditriflate **217** allows the formation of a stable monocoupled product **247** in good yield (Scheme 56). The product, an orange solid, can be recrystallized from hot methanol and is stable in the solid state. Thus, an electron withdrawing group (acetyl group in this case) in the *para* position of the aromatic ring would appear to stabilise the monocoupled product **247**, an electron donating group (such as a *para*-methoxy substituent) has the inverse effect.



217 **247**

Scheme 56

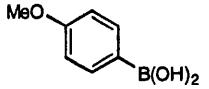
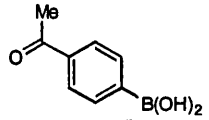
In order to optimise the Suzuki coupling reaction of ditriflate **217** a wide range of inorganic bases were investigated; K_3PO_4, TlOEt, Na_2CO_3 aq and CsF. It was found that the use of CsF as a non aqueous base in dioxane at room temperature provides the coupled product **246** in moderate yields (Table 25). However, when the bases K_3PO_4, TlOEt and Na_2CO_3 were employed in the Suzuki coupling reactions of ditriflate **217** with 4-methoxyphenylboronic acid no reaction occurred.



217

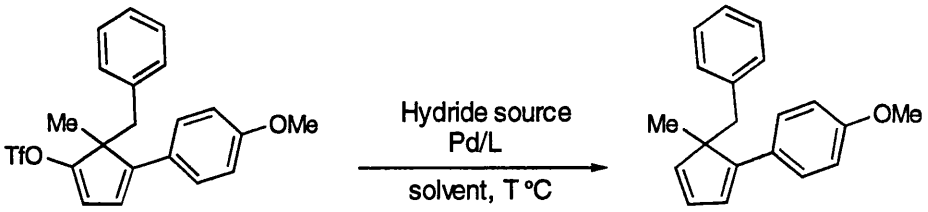
246, R = OMe
247, R = MeCO

Table 25: Suzuki cross-coupling of ditriflate **217** [a]

	Base	Solvent	Time (h)	Yield of product [b] (%)
	CsF	Dioxane	3.25	61
	KOH	THF/H_2O	1-2	31-75
	CsF	Dioxane	3	54
	KOH	THF/H_2O	2	59

[a] Reactions were carried out with 1.25 eq of KOH or 3.0 eq of CsF.
[b] Isolated yield after purification by flash column chromatography.

To circumvent the problem of instability encountered with monocoupled product **246**, a second palladium catalysed cross-coupling reaction was performed on the remaining triflate. The reaction selected was the hydrogenolysis of the triflate moiety which would deliver a cyclopendiene substrate (Table 26). A range of hydride sources have been reported, including tinhydride (Bu_3SnH and Ph_3SnH),[188] a combination of HCOOH and trialkylamine,[189,190] silyl hydrides (Et_3SiH and $(Me_3Si)_3SiH$) and boranes including catecholborane, 9-BBN and BH_3. The hydrogenolysis of triflate **246** was attempted using tributyltin hydride and a mixture of formic acid and tri-*n*-butylamine. The results are shown in Table 26.



246 **248**

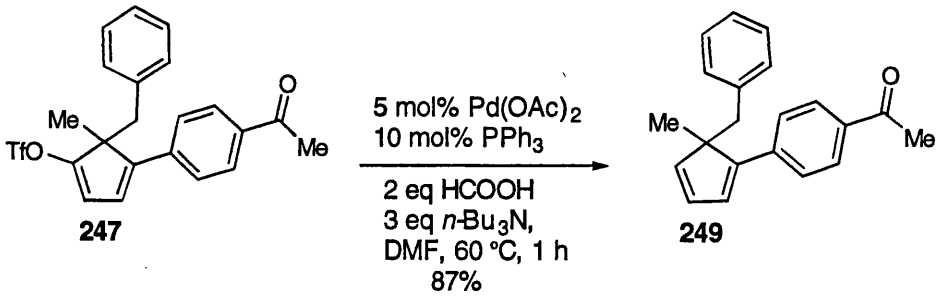
Table 26: Hydrogenolysis of triflate **246** with hydride sources

Hydride source	Pd/L	Addit.	Solvent, T °C	Time (h)	Yield of **248**[a] (%)
$HSnBu_3$, 1.5 eq	$Pd_2(dba)_3$/TFP 10 mol%	LiCl, 3eq	THF, rt	18	0
HCOOH, 2.0 eq	$Pd(OAc)_2/PPh_3$ 5 mol%	*n*-Bu_3N, 3 eq	DMF, 60	1	75

[a] Isolated yield after purification by flash column chromatography.

The reduction of triflate **246** with tributyltin hydride in THF at room temperature was unsuccessful, despite the hydrogenolysis of triflates having been reported as being an efficient reaction.[191] Only homocoupled ditin compound Bu_3Sn-$SnBu_3$ (visible by tlc) and starting material were observed by tlc. Fortunately, the use of the hydride source HCOOH seemed to be more appropriate for triflate **246**. The reaction was complete in one hour and provided the desired cyclopentadiene **248** in 75% yield. The product is a yellow crystalline solid which is stable in air or in solution.

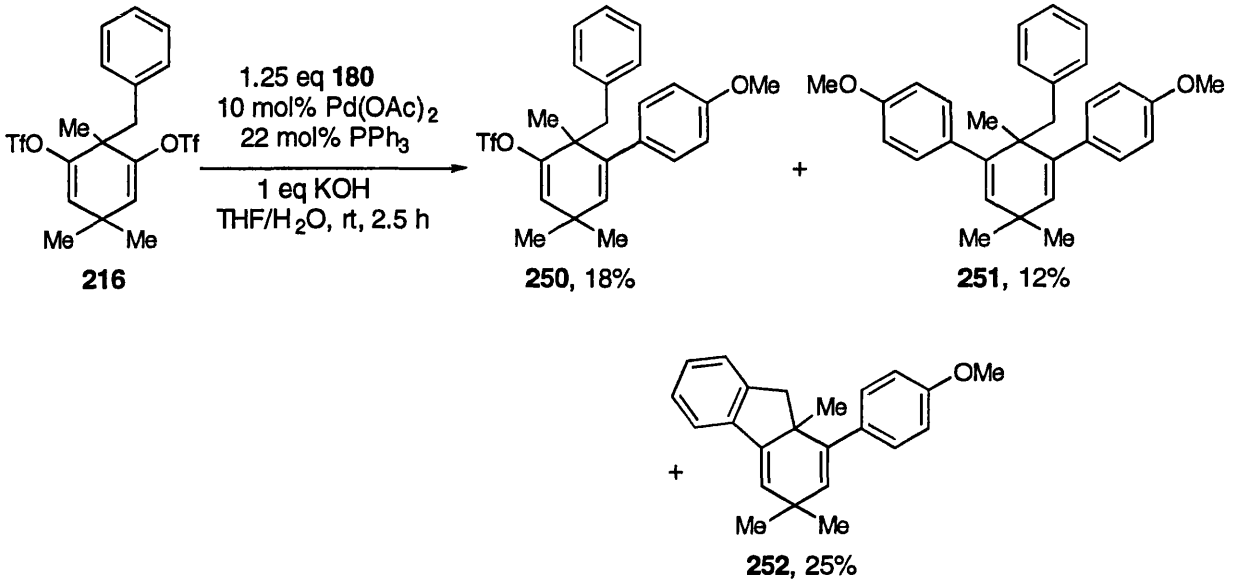
The reduction of triflate **247** with HCOOH in DMF delivered in the same manner the diene **249** in 87% yield (Scheme 57).



247 **249**

Scheme 57

Finally, the reactivity of dimethylated ditriflate **216** in Suzuki cross-coupling reactions was investigated. The substrate was reacted in the presence of 4-methoxyphenylboronic acid **180**, $Pd(OAc)_2$, triphenylphosphine and potassium hydroxide in THF/H_2O for 4 h at room temperature (Scheme 58).

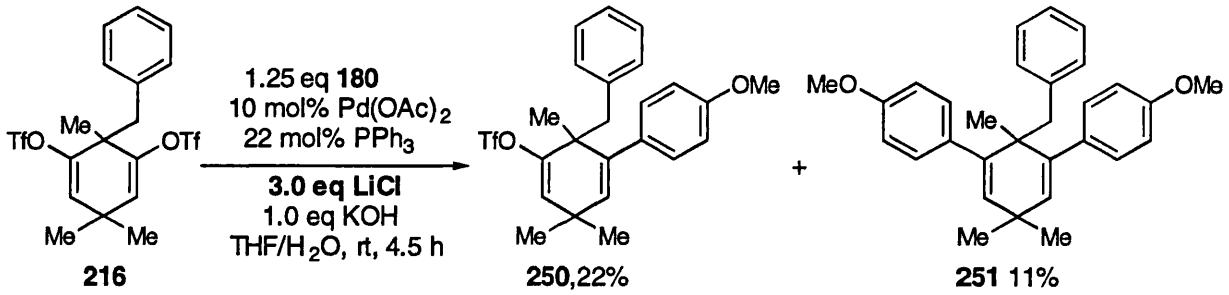


Scheme 58

The Suzuki coupling reaction of ditriflate **216** was almost complete within 2.5 h at room temperature. Four compounds were isolated after purification by flash chromatography of the crude reaction; recovered starting material (6%), the monocoupled product **250** (18%), the dicoupled product **251** (12%) along with a non expected product **252**. This by-product which is slightly less polar than monocoupled product **250** possess a ^1H NMR similar to the NMR spectra of monocoupled product **250**, however the signals in the two spectra present different chemical shifts. The ^{13}C NMR of the non expected product **252** does not show the presence of a triflate group (CF_3 carbon shows a quartet around 118 ppm with a coupling constant between the carbon and the fluorine atom of 319 Hz, C-OTf carbon appears at about 150 ppm). The OTf group stretch is also absent in the IR spectrum. The compound was identified as arising from the intramolecular arylation of product **250** as it had been previously observed with monotriflate **214**. The

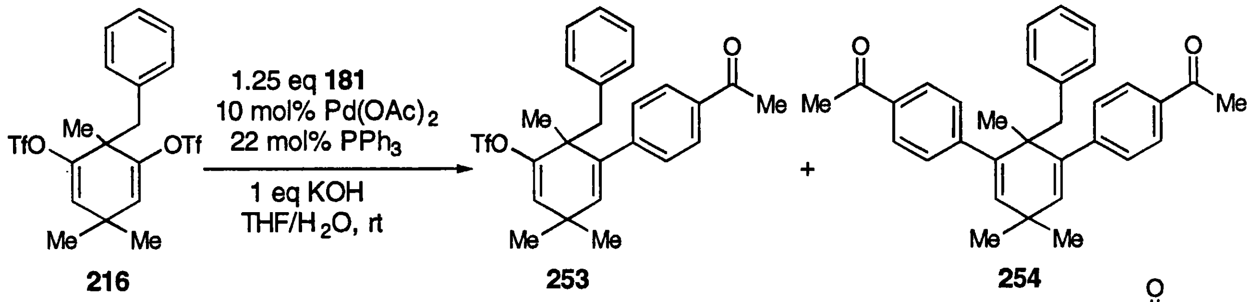
use of an excess of 4-methoxyphenylboronic acid **180** (2.5 eq) provided even larger amount of this tricyclic product **252** and the dicoupled product **251** (25% yield). No monocoupled product **250** was isolated under these conditions.

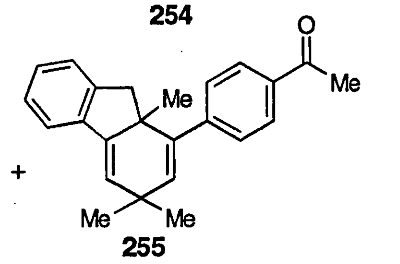
The formation of this by-product **252** can be controlled by carrying out the reaction with or without lithium chloride. Thus, the Suzuki reaction of ditriflate **216** with 1.25 eq of arylboronic acid **180** and 3.0 eq of LiCl provides after, 5.5 h at room temperature, the exclusive formation of the mono and dicoupled product **250** and **251** (with 41% of recovered starting material) (Scheme 59).



Scheme 59

The Suzuki coupling of ditriflate **216** with 4-acetylphenylboronic acid **181** (1.25 eq), $Pd(OAc)_2$ and triphenylphosphine in THF also provided the expected mono and dicoupled product **253** and **254** in moderate yields. A third product **255** was isolated and found to be the product from the intramolecular arylation of **253** (Scheme 60). The amount of this by-product increases with time (as judged by tlc), thus for a complete reaction (15 h) the yield of this tricyclic compound **255** is 31% yield.

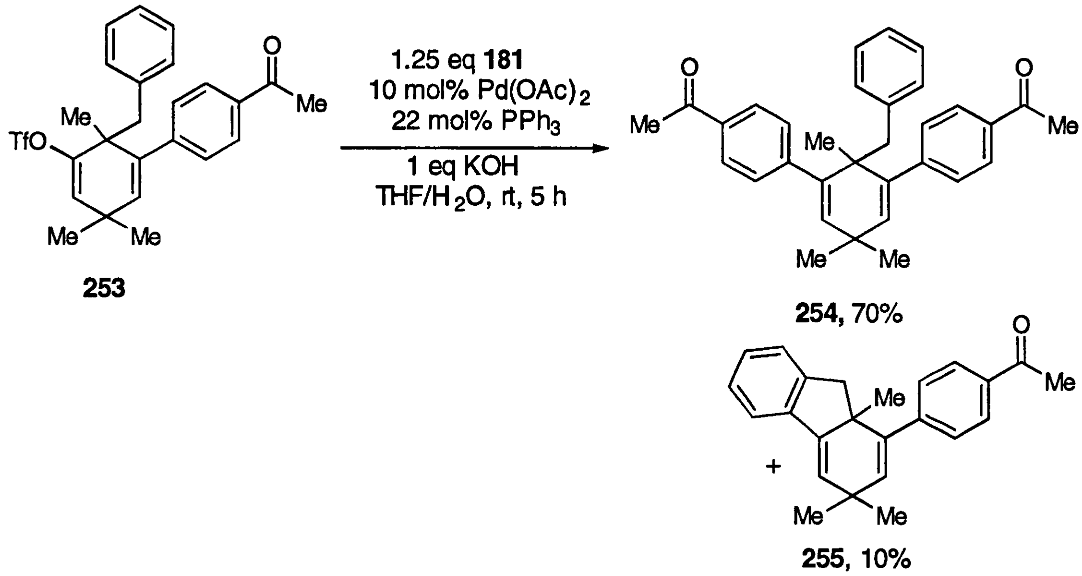




Time (h)	Recovered **216** (%)	Yield of **255** (%)	Yield of **253**(%)
5.5	22	25	10
15	0	31	12

Scheme 60

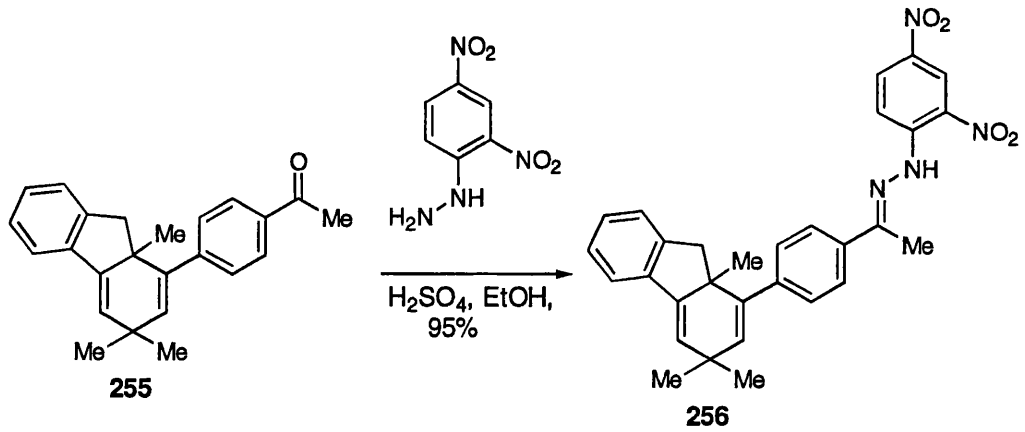
Exposure of monocoupled product **253** to a second Suzuki cross-coupling employing 1.25 eq of arylboronic acid **181**, $Pd(OAc)_2$ and triphenylphosphine in THF for 5 h at room temperature led to the formation of two products; the dicoupled product **254** (70%) and the tricyclic compound **255** (10%) (Scheme 61). However the reaction was not complete (6% recovered starting material) because the palladium catalyst was precipitated as palladium black.



Scheme 61

The very mild conditions required for this intramolecular arylation of ditriflate **216** are as mentioned earlier very exceptional. The monosubstitution of the ditriflate **216** in a Suzuki coupling reaction appears essential prior to the intramolecular reaction; treatment of ditriflate **216** with palladium diacetate and triphenylphosphine in THF afforded only traces of cyclised compound. The substitution of one of the triflate groups with an aryl group in the starting material **216** may favour a spacial arrangement of the molecule where the benzyl group is close to the remaining triflate, thus making the coupling more likely to happen.

Tricyclic compound **255** was treated with 2,4-dinitrophenyl hydrazine in the presence of acid following a literature procedure (Scheme 62).[192] The crude hydrazone was recrystallised from ethanol to give orange crystals of pure hydrazone **256.**



Scheme 62

The X-ray crystal structure (Figure 28) of this hydrazone confirmed the expected structure of the compound **255**.

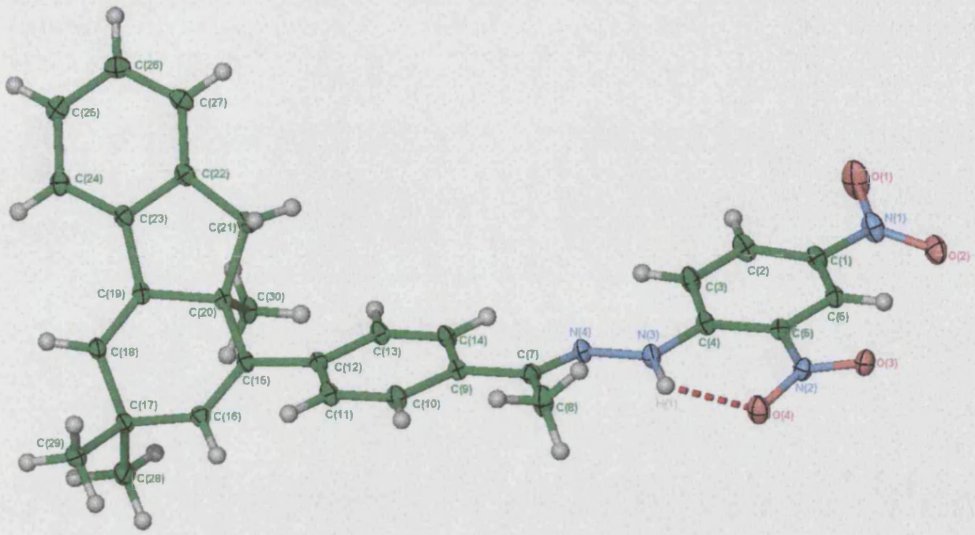


Figure 28

Conclusion

The monotriflates and ditriflates possess very different reactivity towards Suzuki cross-coupling reactions with achiral palladium catalysts. The Suzuki coupling reaction of monotriflate **208** under mild conditions is complete within 40 minutes whereas the corresponding ditriflate **209** is almost unreactive in these conditions. The five- membered ring monotriflate **215** shows poor reactivity in Suzuki cross-coupling reactions with the formation of a by-product **218** in low to moderate yields. However, the reactions of the corresponding ditriflate **217** with arylboronic acids catalysed by palladium are complete within 1 to 3 h at room temperature. Finally, dimethylated mono and ditriflates **214** and **216** were found to be very reactive in Suzuki coupling

reactions, however, in both cases a novel intramolecular coupling catalysed by palladium was observed.

With this information in hand, the enantioselective desymmetrisation reactions of ditriflates **209** and **217** were investigated employing a wide range of chiral catalysts. The kinetic resolution of monotriflate **208** in palladium Suzuki coupling reactions will also be discussed.

Palladium coupling reactions of mono and ditriflates with chiral catalysts

Kinetic resolution studies of monotriflate substrates

Introduction

The first example of kinetic resolution appeared in 1858 when Pasteur investigated fermentation of an aqueous solution of racemic ammonium tartrate by a *Penicillium glaucom* mold.[193] He reisolated the remaining tartrate and found that it was optically active (levatory). Kinetic resolution can be defined as a process in which one enantiomer of a racemic mixture (R:S=1:1) is more readily transformed into a product than is the other (Figure 29).

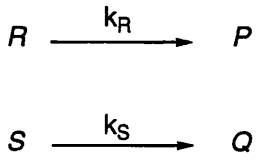
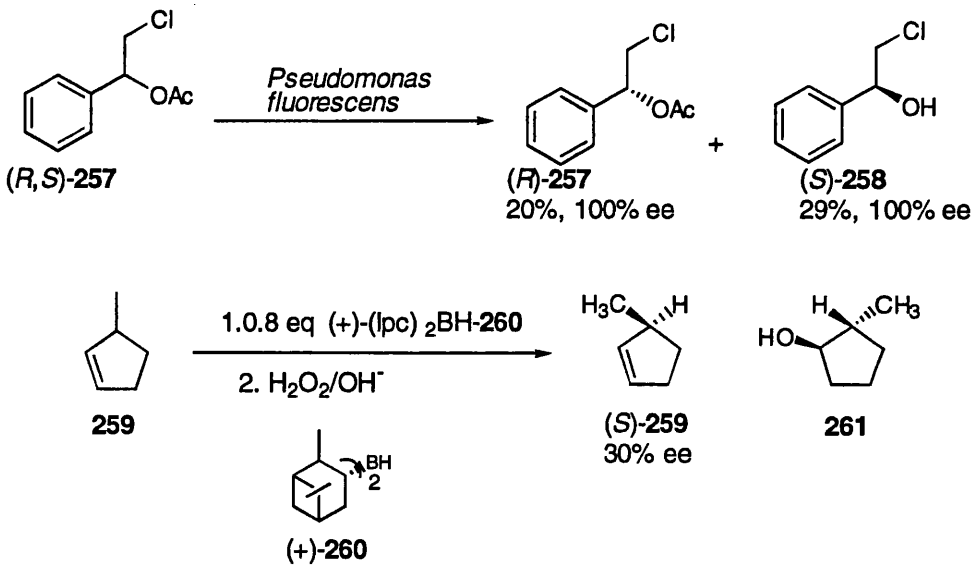


Figure 29

Kinetic resolution occurs if $k_R \neq k_S$ and the reaction is stopped at some stage between 0 and 100% conversion. The ideal situation is that in which only one enantiomer reacts, for example *R* ($k_R >> k_S$) so that a 50% conversion to a mixture of 50% of *S* enantiomer

and 50% product *P* is obtained. The products *P* and *Q* can be achiral (identical or not) or chiral (with or without incorporation of a moiety derived from the chiral reagent). Kinetic resolution can be carried out with various chiral auxiliary compounds (organic, organometallic or enzymatic) and can be catalytic or stoichiometric.[194,195] For example enzyme *Pseudomonas fluorescens* selectively hydrolyses racemic acyloxy-2-chloro-1-phenylethane **257** to give optically pure (*S*)-2-chloro-1-phenylethanol **258** and unreacted (*R*)-**257** in 100% ee (Scheme 63).[196] The reaction of racemic 3-methylcyclopentene **259** with 0.8 equivalent of (+)-$(Ipc)_2BH$ **260** leaves (*S*)-(-) **259** in 30% ee.[197,198]

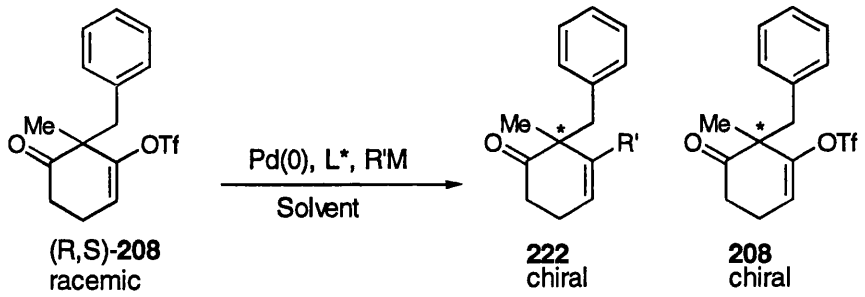


Scheme 63

Results

Our interest is focused on the study of the kinetic resolution of racemic monotriflate **208** in palladium catalysed reactions (Scheme 64). The reaction of substrate **208** with a chiral palladium catalyst and an organometallic reagent R'M would hopefully

selectively occur with one the two enantiomers to give product **222** in good ee, leaving the other antipode of **208** in enantiomerically enriched form.



(R,S)-**208** racemic

222 chiral

208 chiral

Scheme 64

The Suzuki cross-coupling reaction employing 4-methoxyphenylboronic acid **180** was selected to investigate the kinetic resolution of monotriflate **208** as described in Table 27. The palladium catalyst was prepared *in situ* from 10 mol% of $Pd(OAc)_2$ and 10 to 20 mol% of a chiral ligand. The base employed for the couplings was a freshly prepared aqueous solution of 10% KOH. The conversion of the reactions was calculated by ^1H NMR of the crude reaction mixture from the ratios of the integration of the vinylic proton of the starting material and the product. The enantiomeric excess of both monotriflate and coupled product were determined by chiral HPLC utilising an OD column. The results are shown in Table 27.

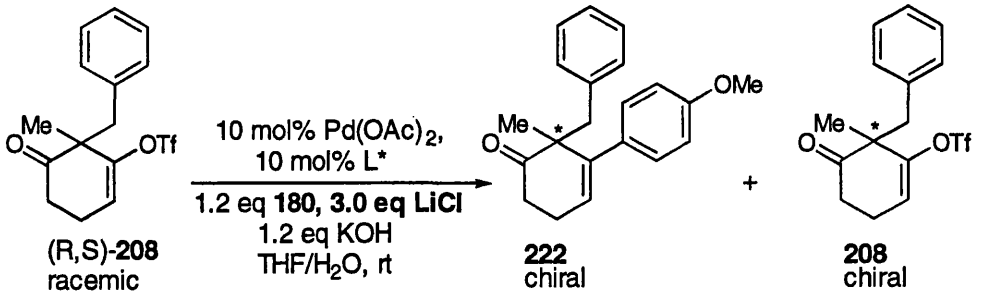
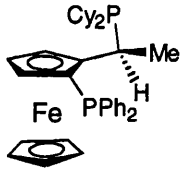


Table 27: Kinetic resolution of monotriflate **208** *via* Suzuki coupling with LiCl

Entry	L*	Time (h)	Conversion [a] (%)	ee[b] of **208** (%)	ee[b] of **222** (%)
1	(*R*)-**4**	13	44.5	7	0
2[c]	(*R*)-**4**	13	28	0	0
3	(*S*)-**104**	25	0	0	0
4	(*R*)-**34**	13	14	2	0
5	(*R*)-**186**	13	66	<1	0
6	(*R,S*)-**262**	16	34	4	4
7[d]	(*S*)-**118**	16	58	0	2
8	(*R*)-**35**	16	73	5	0

[a] Conversion was determined by 1H NMR. [b] Ee's were determined by chiral HPLC (chiralcel OD column). [c] Reaction was carried out with 0.6 eq of **180**.
[d] Reaction was carried out with 30 mol% of (S)-MeO-MOP.



(*R*)-(*S*)-JOSIPHOS **262**

The kinetic resolution of monotriflate **208** in Suzuki cross-couplings was not very successful in terms of enantioselectivity. Even though the conversions of the reactions were good with most of the chiral phosphines used, the enantioselectivities of both remaining starting material and coupled product were very low. The use of the *P,N* ligand *i*-Pr-phosphinoxazoline **104** did not provide any product **222**, even when 20 mol% of the chiral ligand was employed.

The study of monotriflate **208** with achiral catalysts in Suzuki cross-coupling reactions highlighted the effect of lithium chloride; its use slows down the reaction rate of the couplings and moreover the conversion of the reactions were not complete. The kinetic

resolution of monotriflate **208** in Suzuki cross-coupling reactions without using lithium chloride was further investigated. The reactions were performed as described before, employing 10 mol% of $Pd(OAc)_2$, 10 mol% of chiral catalyst with 1.25 equivalent of 4-methoxyphenylboronic acid **180** in THF at room temperature. The results are shown in Table 28.

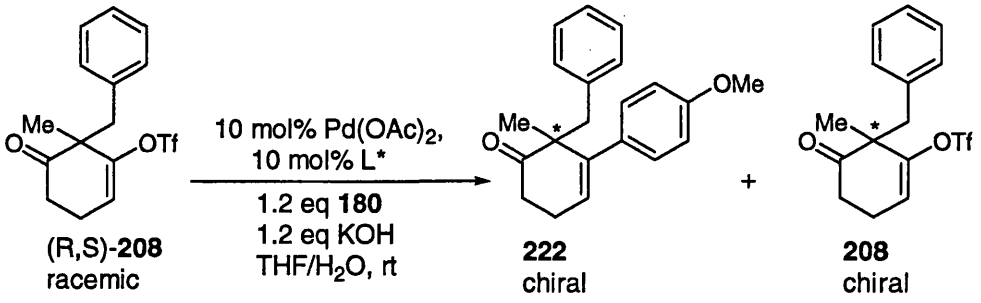
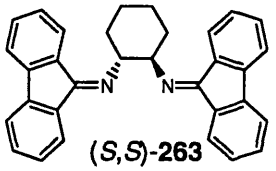


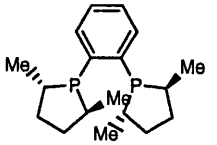
Table 28: Kinetic resolution of monotriflate **208** *via* Suzuki coupling without LiCl

Entry	L*	Time (h)	Conversion[a] (%)	ee[b] of 208 (%)	ee[b] of 222 (%)
1	(*R*)-**4**	15	24	7	0
2	**263**	15	11	0	0
3	(*R*)-(*R*)-**264**	4	7	0	19
4[c]	(+)-**265**	2	88	8	0
5	**266**	2	45	1	0

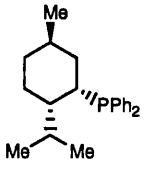
[a] Conversion was determined by ^1H NMR. [b] Ee's were determined by chiral HPLC (chiralcel OD column). [c] Reaction was carried out with 20 mol% of ligand.



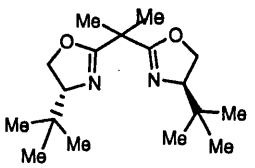
(*S*,*S*)-**263**



(*R*)-(*R*)-Me-DUPHOS **264**



(+)-Neomenthyldiphenyl phosphine **265**



t-Bu-BOX **266**

The use of ligands 2,2'-*iso*propylidene*bis*[(4*S*)-4-*t*-butyl-2-oxazoline] (*t*-Bu-BOX) **266** and (1*S*,2*S*)-*N*,*N*-di(9H-fluoren-9-ylidene)-1,2-cyclohexanediamine **263** provided the coupled product **222** in moderate yields and in racemic form (Entries 2 and 5). Monophosphine ligand (+)-neomenthyldiphenylphosphine **265** was found to be an

efficient ligand, thus providing high conversion of the reaction (88%) but unfortunately no enantioselectivity was observed for the remaining triflate **208** nor the coupled product **222**. The hindered and electron rich phosphine (*R*),(*R*)-Me-DUPHOS **264** gave a very low yield of desired product **222** (7% conv.) with moderate enantiomeric excess (19% ee); this was the highest enantioselectivity observed. An optimisation of the kinetic resolution of triflate **208** was attempted employing a combination of $Pd(OAc)_2$ and chiral catalyst (*R*),(*R*)-Me-DUPHOS **264** in various solvents (Table 29).

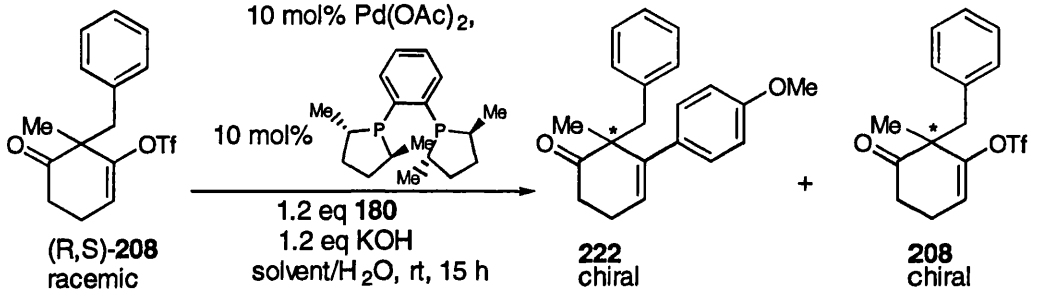


Table 29: Kinetic resolution of monotriflate **208** *via* Suzuki coupling reaction in various solvents

Solvent	Conversion [a] (%)	ee[b] of **208** (%)	ee[b] of **222** (%)
THF	7	7	19
Toluene	8	0	3
Dioxane	17	0	5
DMF	0	-	-
Et_2O	0	-	-

[a] Conversion was determined by ^1H NMR. [b] Ee's were determined by chiral HPLC (chiralcel OD column).

The use of the very polar solvent DMF was unsuccessful for the Suzuki cross-coupling of triflate **208** since no reaction occurred after 18 h at room temperature. The reaction performed in the less polar solvent diethyl ether was also unsuccessful. When dioxane was used as solvent, the conversion increased (17% conv.) at the expense of the enantioselectivity which was very low (5% ee observed for the coupled product **222**).

This improved conversion may be due to the good miscibility of dioxane with water, which enhances the solubility of the inorganic base.

Conclusion

The kinetic resolution of triflate **208** employing a Suzuki-Miyaura cross-coupling reaction with various chiral palladium catalysts delivered the coupled product in poor to good yields (7-88%). However, in most cases the remaining starting material and the expected product were found to be racemic. The highest enantioselectivity was observed with chiral diphosphine (*R*),(*R*)-Me DUPHOS **264** where the product was formed in 19% ee. It appears that the triflate selected for kinetic resolution was not a good substrate since the two enantiomers seem to react with nearly the same reaction rate, thus delivering the desired product in racemic form.

Enantioselective desymmetrisation of ditriflate substrates

Six membered-ring ditriflate

The enantioselective desymmetrisation of ditriflate **209** was studied by carrying out Suzuki cross-coupling reactions with chiral catalysts. It was hoped that monocoupled product **240** which is no longer symmetric would be formed with high enantioselectivity. The reactions were performed in THF, employing 4-methoxyphenylboronic acid **180** and a mixture of $Pd_2(dba)_3$ and a chiral ligand (Table 30).

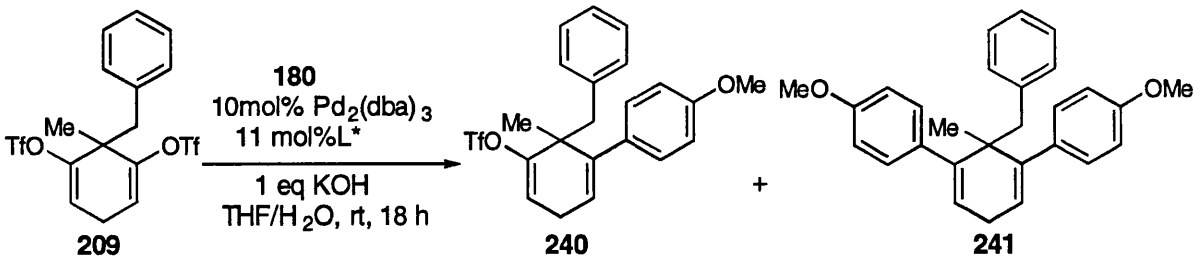


Table 30: Enantioselective Suzuki cross coupling of ditriflate **209**

Entry	L*	recov. **209**[a] (%)	Yield of **240**[a](%)	Yield of **241**[a] (%)	ee of **240**[b] (%)
1	(*R*),(*S*)-**262**	100	0	0	-
2	(*R*)-**4**	20	2	11	2
3	(*R,R*)-**34**	23	3	20	37
4	(*R*)-**105**	26	<1	26	46
5	**266**	31	12	nd	0

[a] Isolated yield after purification by flash column chromatography.
[b] Ee's were determined by chiral HPLC (chiralcel OD column).

In all the conditions selected to investigate the enantioselective Suzuki cross-coupling reactions of ditriflate **209** the same poor reactivity of the substrate was noticed as was described in the study of the ditriflate with achiral catalysts. The use of chiral ferrocene diphosphine ligand (*R*),(*S*)-JOSIPHOS **262** in the enantioselective Suzuki cross-coupling reaction did not afford any products and only starting material was recovered after 18 h at room temperature. The cross-coupling reaction performed with (*R*)-BINAP **4** gave monocoupled product **240** in poor yield (2%) and disappointing low enantiomeric excess. The ligand *t*-Bu-BOX **266** when used in combination with $Pd_2(dba)_3$ afforded the monocoupled product **240** with the highest yield (12%) but in racemic form (Entry 5). The two diphosphine ligands (*R,R*)-DIOP **34** and (*R*)-[2,2]-PHANEPHOS **105** were found to give the highest enantioselectivities (37% and 46% ee respectively) but in very poor chemical yields (Entries 3 and 4).

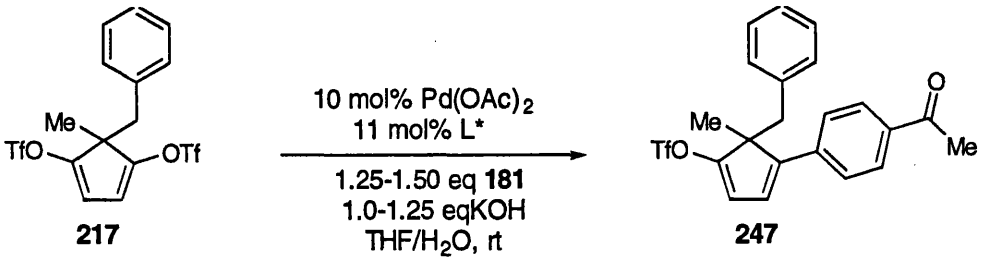
From the study it was concluded that the enantioselective desymmetrisation of ditriflate **209** in Suzuki coupling reaction provides the monocoupled product **240** in good

enantioselectivity (up to 46% ee), however the poor reactivity of the substrate in the basic conditions required for the couplings was unsatisfactory.

Five membered-ring ditriflate

The enantioselective desymmetrisation of ditriflate **217** was investigated in Suzuki cross-coupling reactions with chiral catalysts. 4-Acetylphenylboronic acid **181** was preferred as the coupling partner since the monocoupled product formed is stable and thus would be suitable to carry out HPLC analyses. The reactions were performed in THF employing $Pd(OAc)_2$ (10 mol%) and a bidentate ligand (11 mol%) (Table 31).

The bidentate ligands (*R*)-BINAP **4**, (*R*)-QUINAP **267**, *i*-Pr-PHOX **104**, (*R,R*)-Me-DUPHOS **264** and *t*-Bu-BOX **266** were found to be inefficient in the Suzuki cross-coupling reactions of ditriflate **217** since only starting material was recovered even after 18 h at room temperature (Entries 1, 4, 8 and 9). The use of chiral diphosphine (*R*)-DIOP **34** enables the formation of the coupled product in moderate enantioselectivity (24% ee) and very low chemical yield (Entry 6). (*R*)-[2,2]-PHANEPHOS **105** ligand was found to give the highest chemical yield (38% yield) of desired product **247**, but the asymmetric induction of the reaction was very poor (Entry 3). The enantioselective Suzuki coupling reaction of ditriflate **217** employing (*S*)-MeO-MOP **118** ligand as a bidentate ligand (coordination with the phosphine and the oxygen of the methoxy group) occurred with the highest enantioselectivity (55% ee).

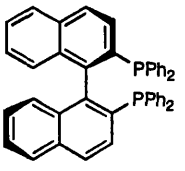


217 247

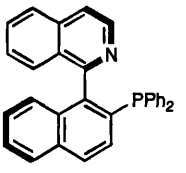
Table 31: Enantioselective Suzuki couplings of ditriflate **217** with bidentate ligands

Entry	Conditions [a]	L*	Time (h)	recovered **217**[b] (%)	Yield of **247** [b](%)	ee of **247** [c] (%)
1	a	(*R*)-**4**	18	100	-	-
2	a	(S,*S*)-**191**	2.5	nd	5	3.5
3	b	(*R*)-**105**	5	31	38	12
4	b	(*S*)-**104**	18	100	-	-
5	b	(*S*),(*R*)-**262**	18	73	trace	nd
6	b	(*R*)-**34**	5	74	6	24
7	b	(*R*)-**267**	5	65	trace	nd
8	b	(*R*,*R*)-**264**	18	100	-	-
9	b	**266**	18	100	-	-
10	**b**	**(S)-118**	**4**	**27**	**25**	**55**

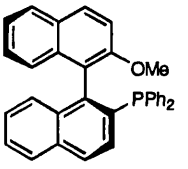
[a] Conditions a: 1.25 eq of boronic acid and 1.25 eq of base, conditions b: 1.5 eq of boronic acid and 1.0 eq of base.[b] Isolated after purification by flash column chromatography.
[c] Ee's were determined by chiral HPLC (chiralcel OD column).



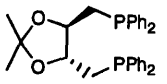
(R)-**4**



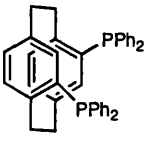
(*R*)-QUINAP **267**



(*S*)-MeO-MOP **118**



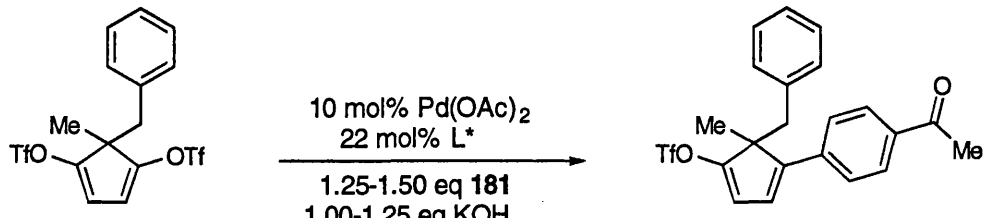
(-)-DIOP **34**



(*R*)-[2,2]-PHANEPHOS **105**

The desymmetrisation of ditriflate **217** employing monodentate ligands was next studied (Table 32). No reaction occurred when (*R*)-QUINAP **267** was used in combination with palladium diacetate (Entry 2). Moderate conversion was observed (29%) with neomenthyldiphenyl phosphine ligand **265**, however the selectivity in this case was very poor (Entry 1). The use of SEMI-ESPHOS[199] **268** or monophosphite[200-

[202] **269** delivered the monotriflate **247** in moderate yield (46 and 41% respectively) with low enantiomeric excess (14 and 12% respectively). The highest enantioselectivity was observed with monophosphine (*S*)-MeO-MOP **118**. Thus the enantioselective desymmetrisation of ditriflate **217** with **118** gave 32% of monosubstituted product **247**, with an encouraging 65% ee.

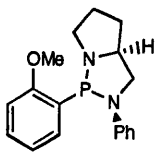


217 **247**

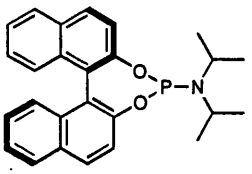
Table 32: Enantioselective Suzuki coupling reactions of ditriflate **217** withmonodentate ligands

Entry	Conditions [a]	L*	Time (h)	recovered **217** [b] (%)	Yield of **247** [b](%)	ee of **247** [c] (%)
1	a	(+)-**265**	4	nd	29	6
2	a	(*R*)-**267**	18	100	-	-
3	b	**268**	5	23	46	14
4	b	(*S*)-**269**	4	28	41	12
5	**b**	(S)-**118**	**4**	**39**	**32**	**65**

[a] Conditions a: 1.25 eq of boronic acid and 1.25 eq of base, conditions b: 1.5 eq of boronic acid and 1.0 eq of base. [b] Isolated after purification by flash column chromatography.
[c] Ee's w ere determined by chiral HPLC (chiralcel OD column).



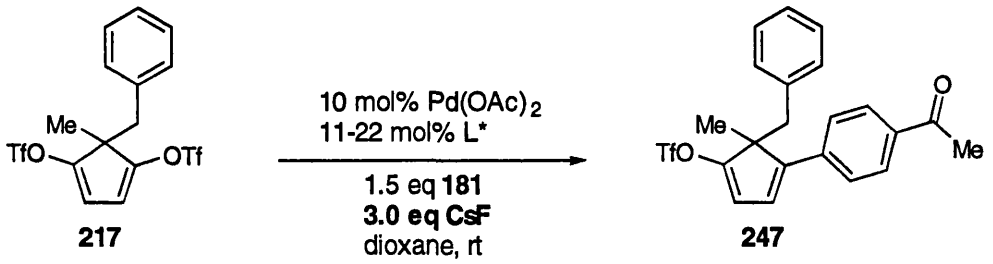
SEMI-ESPHOS **268**



(*S*)- **269**

Finally, the enantioselective desymmetrisation of the ditriflate was performed in non-aqueous conditions in order to study the influence of water on the enantioselectivity of the reactions. The reactions were carried out with 4-acetylphenyl boronic acid **181**, and CsF (3 eq) in dioxane at room temperature. The reactions were catalysed by a palladium catalyst prepared *in situ* from $Pd(OAc)_2$ and the ligands which gave the highest enantioselectivities in the previous studies (Table 31 and 32).

The reactions performed with CsF (instead of aqueous potassium hydroxide) were found to proceed in general with higher enantioselectivity. The enantiomeric excesses were in general improved by 10 to 20% ee. However a decrease in the enantioselectivity of the product **247** was noticed when ligand (*S*)-MeO-MOP (22 mol%) was employed with CsF (the ee dropped from 55 to 52% ee, Entry 5). The best result was still observed with ligand (*S*)-MOP (11 mol%) when the monocoupled product was isolated in 27% yield and an excellent 71% ee (Entry 5). Recrystallisation of the monoproduct **247** of 71% ee from DCM/hexane afforded **247** in 97% ee. The crystal structure of recrystallised **247** indicated a (*S*) conformation of the quaternary carbon.



217 247

Table 33: Enantioselective Suzuki couplings of ditriflate **217** with CsF base

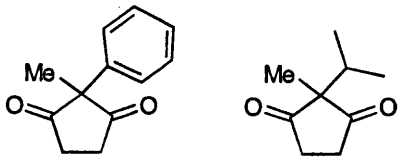
Entry	L*	Time (h)	recovered **217**[a](%)	Yield of **247** [a](%)	ee of **247** [b] (%) (abs. conf.)
1	(*R*)-**105**, 11mol%	3	nd	24	31 (*R*)
2	**268**, 22 mol%	4	50	27	33 (*S*)
3	(S)-**269**, 22 mol%	4	63	17	24 (*R*)
4	**(S)-118, 11 mol%**	**4**	**50**	**27**	**71 (*S*)**
5	(*S*)-**118**, 22 mol%	4	31	38	52 (*S*)

[a] Isolated after purification by flash column chromatography.
[b] Ee's were determined by chiral HPLC (chiralcel OD column).

Conclusions and future work

The desymmetrisation of ditriflate **209** and **217** in palladium catalysed Suzuki reactions is possible. Both substrates when reacted with the arylboronic acids **180** or **181** in the presence of a palladium source ($Pd_2(dba)_3$ or $Pd(OAc)_2$), and a chiral ligand deliver the monocoupled products in moderate to good enantioselectivity. However the six membered ring ditriflate **209** showed poor reactivity which limits its use. The equivalent five membered ring ditriflate **217** appears a much more attractive substrate since its reactivity in asymmetric Suzuki cross-coupling reactions is considerably higher. The enantioselective desymmetrisation of ditriflate **217** can deliver the monocoupled product **247** in up to 49% yield (with PHANEPHOS ligand and aqueous KOH) and up to 71% ee (with (*S*)-MeO-MOP, 11 mol% and CsF).

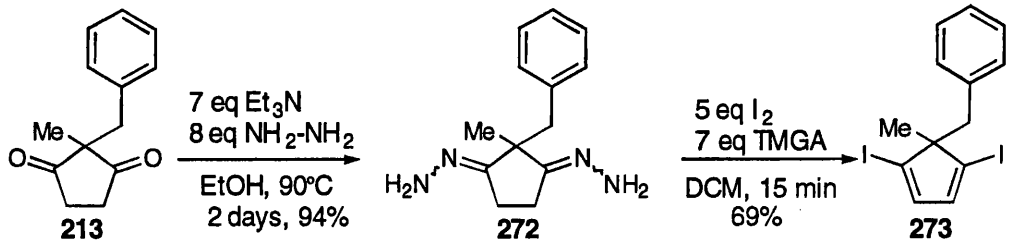
A detailed study regarding the enantioselective desymmetrisation of ditriflate **217** could be carried out (*via* Suzuki cross-coupling reactions) in order to optimise the chemical yields of monocoupled **247** formed. This would include the screening of solvents, the use of oxygen free conditions (degassed solvent) and the use of higher catalyst loadings. The enantioselective palladium catalysed desymmetrisation of analogs to ditriflate **217** where the benzyl is substituted to a much bulkier group should also be investigated. For example diketones such as **270** and **271** which are prepared in a two step synthesis[203,204] could be employed to prepare the equivalent ditriflates (Figure 30). The Stille coupling and methoxycarbonylation reactions of ditriflate **209** both delivered moderate yields of monocoupled products. These reactions could also be envisaged employing ditriflate **217** in achiral and chiral conditions.



270 **271**

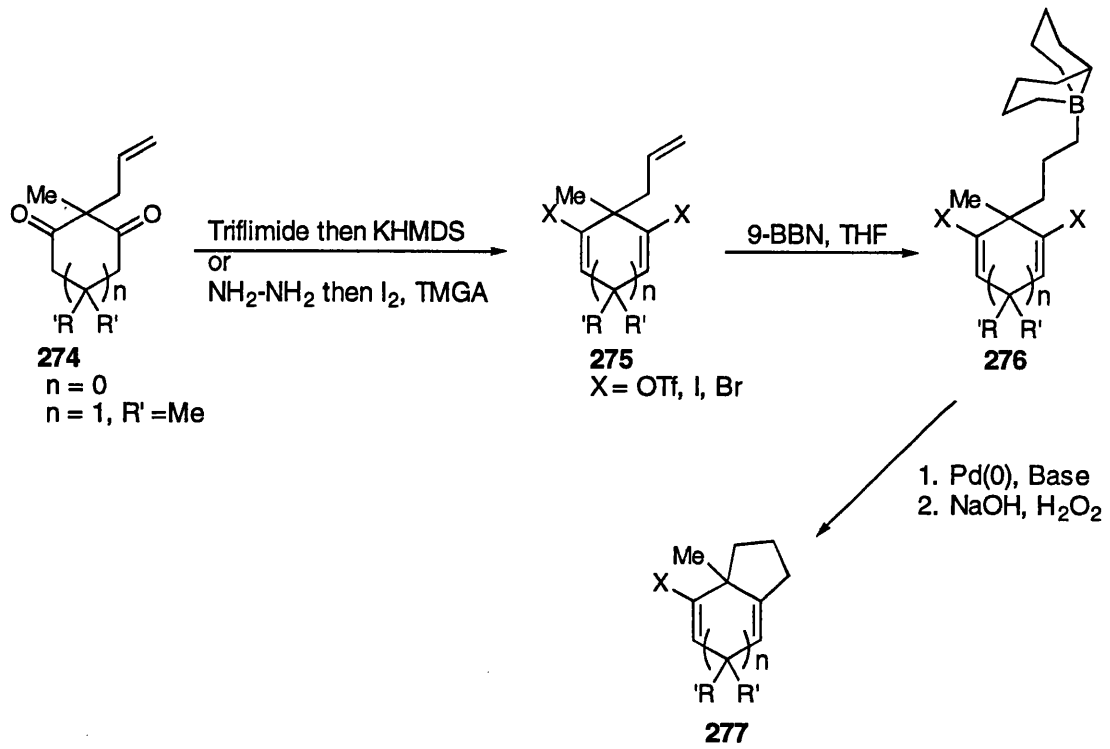
Figure 30

It would also be interesting to carry out a study using analogues of vinyl triflate **217** in which the triflate is repalced by an iodine atom, a bromine atom or a vinyl phosphate group. We have shown that the vinyl iodide **273** is easily prepared in a two-step sequence from the equivalent diketone **213**. Treatment of diketone **213** with monohydrate hydrazine in the presence of triethylamine afforded the dihydrazone **272** in 94% yield (Scheme 65). Vinyl iodide **273** is then formed in good yield when dihydrazone **272** is reacted with tetramethyl guanidine and iodine in DCM.



Scheme 65

Finally, the intramolecular Suzuki cross-couplings of a family of substrates such as **276** could be studied in chiral or achiral conditions to deliver a range of functionalised products **277** (Scheme 66). These substrates could be accessed *via* a two-step sequence from the diketones **274**. The treatment of diketones **274** with either 5-chloro-triflimide **201** and KHMDS or monohydrate hydrazine followed by reaction with iodine and tetramethylguanidine would deliver the vinyl triflate or iodide substrate **275**. The vinyl iodide or triflate could react with 9-BBN to give starting materials **276**.



Scheme 66

Chapter 5: Experimental

General procedures

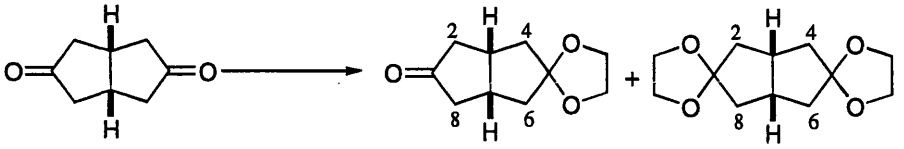
^{1}H NMR spectra were recorded on a JEOL 270 EX, JEOL 400 EX or a Bruker AM-300 spectrometers at 270 MHz, 400 MHz and 300 MHz respectively. Residual protic solvent $CHCl_3$ (δ_H = 7.26 ppm) or TMS (δ_H = 0 ppm) were used as internal references. Coupling constants were measured in Hz. ^{19}F NMR spectra were recorded on a JEOL 400 EX at 376 MHz. ^{13}C spectra were recorded in $CDCl_3$, unless otherwise stated, at 100 MHz, 75 MHz and 67.5 MHz on JEOL 400 EX, Brucker AM-300 and JEOL 270 EX spectrometers respectively, using the resonance of $CDCl_3$ (δ_C = t, 77 ppm) as the internal reference. Infra red spectra were recorded in the range of 4000-600 cm^{-1} on a Perkin Elmer FT 1000 spectrometer with internal calibration. Mass spectra were carried out either at Bath University (Finnigan MAT 8340 instrument) or at the University of Wales Swansea (Finnigan MAT 900 XLT instrument). Melting points were measured on an Büchi 535 melting point apparatus and are uncorrected. High Pressure Liquid Chromatography was performed on SP Thermo Separation products spectra SERIES and Spectra Physics Systems using Chiralcel OD®columns obtained from Fisher Scientific supplies.

Analytical thin layer chromatography was carried out using glass backed plates coated with Merck Kieselgel 60 GF_{254} or aluminium backed plates coated with Merck G/UV_{254}. Plates were visualised under UV light (at 254 nm) or by staining with potassium permanganate, vanillin or cerium ammonium molybdate followed by heating. Flash chromatography was carried out using either Merck 60 H silica or Merck Florisil®. Samples were pre-absorbed on silica or used as saturated solutions in an appropriate solvent.

Tetrahydrofuran and ether were distilled from sodium benzophenone ketyl, toluene from sodium and dimethoxyethane, DCM, DCE, *N*-methylpyrrolidinone and *N,N*-dimethylformamide from CaH_2 all under nitrogen. Dry 1,4 dioxane 99.9% was purchased from Aldrich in a Sure-Seal bottle. Petrol refers to light petroleum, bp 40-60 °C, ether refers to diethyl ether.

Unless otherwise stated, commercially available starting materials were used throughout without any further purification. Thallium hydroxide aqueous 10% solution was prepared according to George's procedure, stored at 5 °C and used within one week.[126] Potassium hydroxide 10% aqueous solution was freshly prepared before use. Triflic anhydride was prepared from triflic acid and P_2O_5 prior to use according to Stang's procedure.[205] 2,6-Di-*tert*butyl-4-methylpyridine was prepared according to Stang's method[206] and *N*-5(chloro-2-pyridyl)triflimide was prepared according to Comin's procedure.[157] 4-Methoxyphenyltributyltin was prepared from (4-methoxyphenyl) magnesium iodide and tributyltin chloride.[183] *Cis*-bicyclo[3.3.0]octane-3,7-dione and *cis*-1,5-dimethyl-bicyclo[3.3.0]octane-3,7-dione were prepared according to Retz's procedure. [134] 2-Benzyl-2-methyl-1,3-cyclohexadione and 2-benzyl-5,5-dimethyl-cyclohexadione were prepared from literature procedures.[164,166] Reactions requiring anhydrous conditions were performed under nitrogen in oven or flame dried apparatus.

Preparation of (3*R,7*S**)-1,5-bis(1,3-dioxolan-2-yl)-*cis*-bicyclo[3.3.0]octane (171) and (3*R**,7*S**)-5-(1,3-dioxolan-2-yl)-*cis*-bicyclo[3.3.0]octan-1-one (169)**

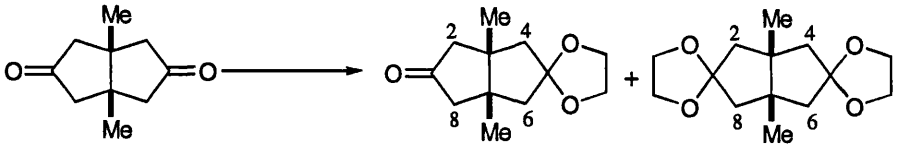


167 **169** **171**

A stirred mixture of diketone **167** (10.00 g, 0.07 mol), ethylene glycol (4.2 mL, 0.07 mol), *p*-toluene sulfonic acid (0.09 g, 0.5 mmol) and toluene (70 mL) was heated at reflux for 2 h with a Dean-Stark water trap. The solution was cooled to room temperature, diluted with ether (70 mL), washed successively with 10% aqueous sodium hydroxide, water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material (a 1:2:1 mixture of diketone:ketoacetal:diacetal) was purified by flash chromatography (33% EtOAc/petrol) to give in order of elution; *diacetal* **171** (8.00 g, 48%) as a white solid, mp 54-55 °C; R_f(petrol:EtOAc 66:33) 0.37; ν_{max} (Nujol)/cm^{-1} 2923(CH), 1114(C-O); δ_H (400 MHz, $CDCl_3$) 3.89 (8H, s, 4 x CH_2-O), 2.62-2.59 (2H, m, H-3, H-7), 1.98 (4H, dd, *J* 13.2, 8.8, H-2a, H-4a, H-6a, H-8a), 1.71 (4H, dd, *J* 13.2, 6.3, H-2b, H-4b, H-6b, H-8b); δ_C (100 MHz, $CDCl_3$) 118.6 (C-1, C-5), 64.5 (2 x CH_2-O), 63.9 (2 x CH_2-O), 41.4 (C-2, C-4, C-6, C-8), 37.0 (C-3, C-7); m/z (EI^+) 226.1 (57%, M^+); Found M^+, 226.1208, $C_{12}H_{18}O_4$ requires 226.1205; *ketoacetal* **169** (5.51 g, 42%) as a yellow oil, R_f(petrol:EtOAc 66:33) 0.20; ν_{max} (neat)/cm^{-1} 2958 (CH), 2888 (CH), 1738 (C=O), 1118 (C-O); δ_H (400 MHz, $CDCl_3$) 3.80 (4H, s, 2 x CH_2-O), 2.73 (2H, m, H-3, H-7), 2.47-2.37 (2H, m, H-2a, H-8a), 2.18-2.07 (4H, m, H-2b, H-4a, H-6a, H-8b), 1.62 (4H, dd, *J* 13.9, 5.3, H-4b, H-6b); δ_C (100 MHz, $CDCl_3$) 219.8 (C-1), 118.0 (C-5), 64.3 (CH_2-O), 63.9 (CH_2-O), 44.1 (C-2, C-8),

42.2 (C-6, C-4), 36.7 (C-3, C-7); m/z (EI$^+$) 182.1 (70%, M^+); Found M^+, 182.0944, $C_{10}H_{14}O_3$ requires 182.0943.

Preparation of (3*R,7*S**)-3,7-dimethyl-1,5-bis(1,3-dioxolan-2-yl)-*cis*-bicyclo [3.3.0] octane (172) and (3*R**,7*S**)-3,7-dimethyl-5-(1,3-dioxolan-2-yl)-*cis*-bicyclo[3.3.0] octan-1-one (170)**

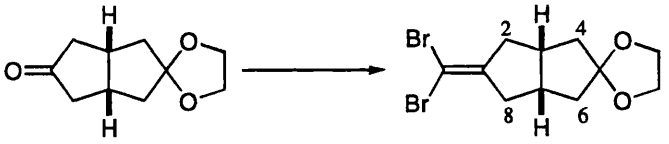


168 **170** **172**

A stirred mixture of diketone **168** (3.50 g, 0.02 mol), ethylene glycol (1.2 mL, 0.02 mol), *p*-toluene sulfonic acid (0.02 g, 0.1 mmol) and toluene (21 mL) was heated at reflux for 3 h with a Dean-Stark water trap. The solution was cooled to room temperature, diluted with ether (30 mL), washed successively with 10% aqueous sodium hydroxide, water and brine, dried ($MgSO_4$) and concentrated under reduced pressure. The crude material (a 1:2:1 mixture of diketone:ketoacetal:diacetal) was purified by flash chromatography (20% EtOAc/petrol) to give in order of elution; *diacetal* **172** (1.12 g, 21%) as a white solid, mp 54-55 °C; R_f(petrol:EtOAc 80:20) 0.36; ν_{max} (Nujol)/cm^{-1} 2957 (CH), 2875 (CH), 1095 (C-O); δ_H (400 MHz, $CDCl_3$) 3.85 (8H, s, 4 x CH_2-O), 2.15 (4H, d, *J* 14.1, H-2a, H-4a, H-6a, H-8a), 1.80 (4H, d, *J* 14.1, H-2b, H-4b, H-6b, H-8b), 1.05 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 116.8 (C-1, C-5), 64.3 (2 x CH_2-O), 64.1 (2 x CH_2-O), 50.2 (C-2, C-4, C-6, C-8), 48.6 (C-3, C-7), 22.3 (2 x CH_3); m/z (FAB$^+$) 255.2 (100%, M+H$^+$); Found M^+, 254.1520, $C_{14}H_{22}O_4$ requires 254.1518; *ketoacetal* **170** (1.68 g, 38%) as a white solid, mp 43-44 °C; R_f(petrol:EtOAc

80:20) 0.24; ν_{max} (Nujol)/cm^{-1} 2960 (CH), 2875 (CH), 1743 (C=O), 1115 (C-O); δ_H (270 MHz, $CDCl_3$) 3.83 (4H, s, 2 x CH_2-O), 2.48 (2H, d, *J* 18.9, H-2a, H-8a), 2.11 (2H, d, *J* 18.9, H-2b, H-8b), 2.01 (4H, s, 2 x H-4, 2 x H-6), 1.00 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 218.4 (C-1), 116.2 (C-5), 63.9 (2 x CH_2-O), 51.1 (C-2, C-8 or C-4, C-6), 49.9 (C-2, C-8 or C-4, C-6), 47.1 (C-3, C-7), 22.0 (2 x CH_3); m/z (FAB$^+$) 211.2 (100%, *M*+H$^+$); Found *M*$^+$, 210.1254, $C_{12}H_{18}O_3$ requires 210.1256.

Preparation of (3*R,7*S**)-1-(dibromomethylene)-5-(1,3-dioxolan-2-yl)-*cis*-bicyclo [3.3.0] octane (147)**

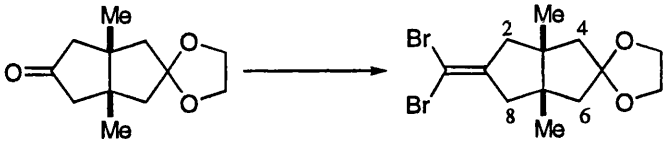


169 **147**

A solution of carbon tetrabromide (7.00 g, 21.1 mmol) in dry toluene (5 mL) was added *via* cannula to a stirred mixture of triphenylphosphine (11.00 g, 43 mmol) in dry toluene (5 mL) under nitrogen at room temperature. The orange solution was stirred for 1 h at room temperature after which time a solution of ketoacetal **169** (1.50 g , 8.25 mmol) in dry toluene (15 mL) was added *via* cannula and the mixture was heated at reflux for 3 h. The dark brown solution was cooled to room temperature, filtered and concentrated under reduced pressure. The residue was triturated with hexane (200 mL) to remove triphenylphosphine oxide, and the solution was filtered and concentrated under reduced pressure to give an orange oil. The residue was purified by flash chromatography (2% EtOAc/petrol) to give *1,1-dibromoalkene* **147** (1.86 g, 67%) as a white solid, mp 52-53 °C; ν_{max} (Nujol)/cm^{-1} 2937 (CH), 2883 (CH), 1641 (C=C), 1117 (C-O); δ_H (400 MHz,

$CDCl_3$) 3.89 (4H, s, 2 x CH_2-O), 2.73-2.69 (2H, m, H-3, H-7), 2.63-2.56 (2H, m, H-2a, H-8a), 2.35-2.29 (2H, m, H-2b, H-8b), 2.05 (2H, dd, *J* 13.7, 8.3, H-4a, H-6a), 1.69 (2H, dd, *J* 13.7, 5.9, H-4b, H-6b); δ_C (100 MHz, $CDCl_3$) 150.7 (CBr_2), 118.7 (C-5), 79.1 (C-1), 64.5 (CH_2-O), 63.9 (CH_2-O), 42.1 (C-4, C-6), 41.9 (C-3, C-7), 41.6 (C-2, C-8); m/z (EI^+) 338.0 (71%, M^+); Found M^+, 337.9330, $C_{11}H_{14}O_2{}^{79}Br^{81}Br$ requires 337.9340.

Preparation of (3*R,7*S**)-1-(dibromomethylene)-3,7-dimethyl-5-(1,3-dioxolan-2-yl)-*cis*-bicyclo[3.3.0]octane (173)**

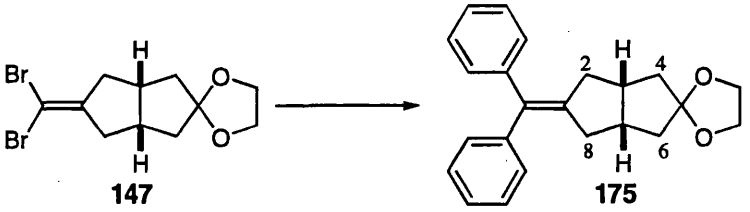


170 **173**

A solution of carbon tetrabromide (4.50 g, 13.5 mmol) in dry toluene (5 mL) was added *via* cannula to a stirred mixture of triphenylphosphine (7.12 g, 27.2 mmol) in dry toluene (4 mL) under nitrogen at room temperature. The orange solution was stirred for 1 h at room temperature after which time a solution of ketoacetal **170** (1.00 g, 4.8 mmol) in dry toluene (10 mL) was added *via* cannula and the mixture was heated at reflux for 22 h. The dark-brown solution was cooled to room temperature, filtered and then concentrated under reduced pressure. The residue was triturated with hexane (150 mL) to remove triphenylphosphine oxide and the solution filtered and solvent was removed under reduced pressure to give an orange oil. The residue was purified by flash chromatography (2% EtOAc/petrol) to give *1,1-dibromoalkene* **173** (1.20 g, 68%) as a white solid, mp 54-55 °C, ν_{max} (Nujol)/cm^{-1} 2924 (CH), 2855 (CH), 1640 (C=C), 1121 (C-O); δ_H (400 MHz, $CDCl_3$) 3.85 (4H, s, 2 x CH_2-O), 2.56 (2H, dd, *J* 17.7, 2.3,

H-2a, H-8a), 2.23 (2H, dd, *J* 17.7, 2.1, H-2b, H-8b), 2.00 (2H, d, *J* 14.6, H-4a, H-6a), 1.88 (2H, d, *J* 14.6, H-4b, H-6b), 1.00 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 148.3 (CBr_2), 116.5 (C-5), 80.0 (C-1), 63.9 (2 x CH_2-O), 50.7 (C-3, C-7), 49.6 (C-2, C-8), 48.2 (C-4, C-6), 21.6 (2 x CH_3); m/z (FAB^+) 367.0 (100%, $(M+H)^+$); Found M^+, 365.9657, $C_{13}H_{18}O_2{}^{79}Br^{81}Br$ requires 365.9653.

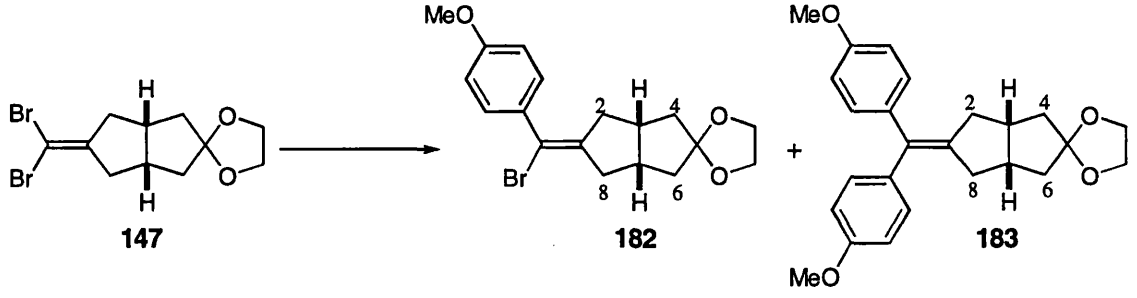
Preparation of (3*R,7*S**)-5-(1,3-dioxolan-2-yl)-1-(diphenylmethylene)-*cis*-bicyclo [3.3.0]octane (175)**



Dry *N*-methylpyrrolidinone (1 mL) was added under nitrogen to a mixture of dibromide **147** (50.0 mg, 0.15 mmol), $Pd(dba)_2$ (8.5 mg, 0.015 mmol, 10 mol%), TFP (6.9 mg, 0.030 mmol), and the resulting solution was stirred for 10 min at room temperature. Trimethyl(phenyl)tin (73 μL, 0.22 mmol) was then added *via* syringe and the mixture was heated at 50 °C for 26 h before cooling to room temperature. The reaction was diluted with EtOAc (3 mL) and saturated KF solution (2 mL) was added and the mixture stirred for 1 h. The layers were separated and the organic phase was washed with water (3 x 2 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The crude material was purified by flash chromatography (5% acetone/petrol) to give in order of elution; recovered starting material **147** (30%) and a mixture of 1,1-diphenylalkene **175** and biphenyl.

Crystallisation of this mixture from hot petrol afforded pure *1,1-diphenylalkene* **175** (22.0 mg, 45%) as a white solid; ν_{max} (Nujol)/cm^{-1} 3052 and 2987 (unsaturated CH), 2924 and 2855 (saturated CH), 1620 (C=C), 1121 (C-O); δ_H (270 MHz, $CDCl_3$) 7.31-7.15 (10H, m, Ar), 3.89 (4H, s, 2 x CH_2-O), 2.64-2.60 (4H, m, H-2a, H-3, H-7, H-8a), 2.34-2.29 (2H, m, H-2b, H-8b), 2.04-1.97 (2H, m, H-4a, H-6a), 1.65 (2H, td, *J*, 13.7, 6.0, H-4b, H-6b); m/z (EI$^+$) 332.1 (25%, M^+); Found M^+, 332.0942, $C_{23}H_{24}O_2$ requires 332.0941.

Preparation of (3*R,7*S**)-1-(bromo(4-methoxyphenyl)methylene)-5-(1,3-dioxolan-2-yl)-*cis*-bicyclo[3.3.0]octane (182) and (3*R**,7*S**)-5-(1,3-dioxolan-2-yl)-1-bis((4-methoxyphenyl)methylene)-*cis*-bicyclo[3.3.0]octane (183)**

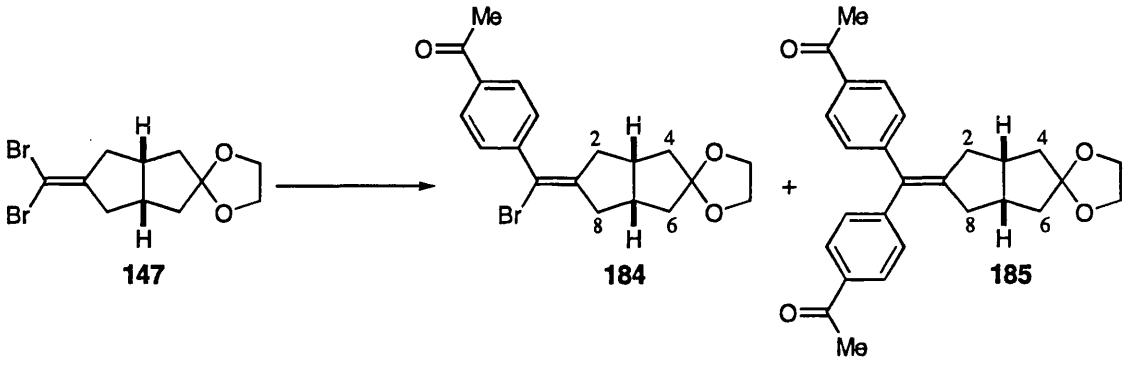


Dry THF (2 mL) was added to a mixture of $Pd(PPh_3)_4$ (17.6 mg, 0.022 mmol, 10 mol%), 1,1-dibromoalkene **147** (75.0 mg, 0.22 mmol) and 4-methoxyphenylboronic acid (42.1 mg, 0.277 mmol) under nitrogen. The resulting solution was stirred for 15 min, then freshly prepared aqueous thallium hydroxide solution (0.4 M, 0.55 mL, 0.22 mmol) was added *via* syringe and the mixture was stirred at room temperature for 2 days. The solution was partitioned between water (3 mL) and EtOAc (3 mL), the layers were separated and the aqueous phase was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced

pressure. The residue (a mixture of starting material, monocoupled product **182** and dicoupled product **183**) was purified by flash chromatography (15% EtOAc/petrol) to give in order of elution; recovered dibromoalkene **147** (27.0 mg, 36%); *monobromoalkene* **182**, (12.1 mg, 15%) as a yellow oil; R_f(petrol:EtOAc 85:15) 0.27; ν_{max} (neat)/cm^{-1} 3032 (unsaturated CH), 2935 (saturated CH), 2834 (O-CH_3), 1600 (Ar C=C), 1113 (C-O); δ_H (400 MHz, $CDCl_3$) 7.31-7.29 (2H, m, Ar), 6.86-6.83 (2H, m, Ar), 3.89 (2H, s, 1 x CH_2-O), 3.88 (2H, s, 1 x CH_2-O), 3.81 (3H, s, CH_3O), 2.82-2.76 (1H, m, 1 x H-2 or 1 x H-8), 2.67-2.61 (2H, m, H-3, H-7), 2.56-2.46 (2H, m, 1 x H-2, 1 x H-8), 2.29-2.24 (1H, m, 1 x H-2 or 1 x H-8), 2.12-2.06 (1H, m, 1 x H-4 or 1 x H-6), 1.99-1.94 (1H, m, 1 x H-4 or 1 x H-6), 1.75 (1H, dd, *J* 13.8, 6.5, 1 x H-4 or 1 x H-6), 1.60 (1H, dd, *J* 14.6, 6.5, 1 x H-4 or 1 x H-6); δ_C (100 MHz, $CDCl_3$) 159.0 (C-OMe), 144.9 (C=C-Br), 133.4 (Ar C), 130.4 (2 x Ar CH), 119.08 (C-5), 113.7 (C-1), 113.5 (2 x Ar CH), 64.9 (CH_2-O), 64.2 (CH_2-O), 55.6 (CH_3-O), 43.0 (CH_2), 42.8 (CH_2), 42.9 (C-3 or C-7), 42.1 (CH_2), 40.4 (C-3 or C-7), 39.1 (CH_2); m/z (EI$^+$) 366.2 (15%, M^+); Found M^+, 364.0674, $C_{18}H_{21}O_3{}^{79}Br$ requires 364.0671 and *diarylalkene* **183** (31.0 mg, 36%) as a yellow oil; R_f(petrol:EtOAc 85:15) 0.21; ν_{max} (neat)/cm^{-1} 3030 (unsaturated CH), 2933 (saturated CH), 2834 (O-CH_3), 1598 (Ar C=C), 1113 (C-O); δ_H (270 MHz, $CDCl_3$) 7.10-7.05 (4H, m, Ar), 6.84-6.79 (4H, m, Ar), 3.89 (4H, s, 2 x CH_2-O), 3.79 (6H, s, 2 x CH_3O), 2.62-2.59 (4H, m, H-2a, H-8a, H-3, H-7), 2.31 (2H, d, *J* 12.9, H-2b, H-8b), 2.00 (2H, dd, *J* 13.5, 6.4, H-4a, H-6a), 1.64 (2H, dd, *J* 13.5, 5.6, H-4b, H-6b); δ_C (100 MHz, $CDCl_3$) 157.9 (2 x C-OMe), 141.4 (C), 136.14 (C), 133.6 (Ar C), 130.6 (4 x Ar CH), 119.0 (C-5), 113.5 (4 x Ar CH), 64.9 (CH_2-O), 64.2 (CH_2-O), 55.5 (2 x CH_3-O), 42.4 (CH_2), 40.6 (C-3, C-7), 38.8 (CH_2); m/z (EI$^+$) 392.3 (35%, M^+); Found M^+, 392.1986, $C_{25}H_{28}O_4$ requires 392.1988.

The enantiomers of **182** were separated by HPLC using a Chiralcel OD column (99:1 hexanes:*iso*propanol), 1 mL/min; t_r = 11.6 min and t_r = 14.7 min.

Preparation of (3*R,7*S**)-1-(bromo(4-acetylphenyl)methylene)-5-(1,3-dioxolan-2-yl)-*cis*-bicyclo[3.3.0]octane (184) and (3*R**,7*S**)-1-bis((4-acetylphenyl)methylene)-5-(1,3-dioxolan-2-yl)-*cis*-bicyclo[3.3.0]octane (185)**

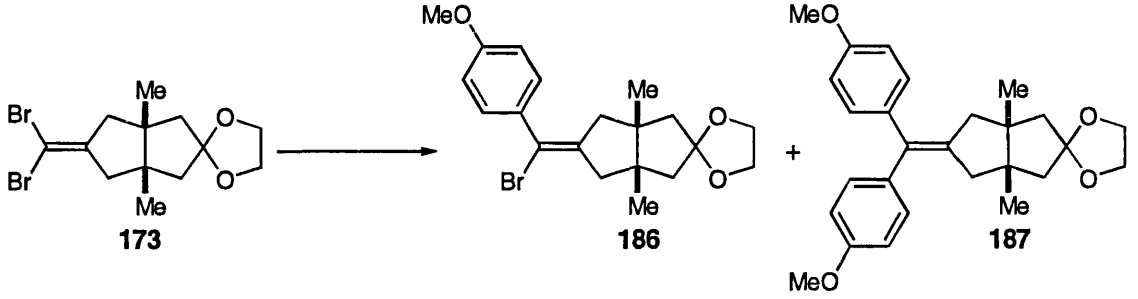


Dry THF (2 mL) was added to a mixture of $Pd(PPh_3)_4$ (23.0 mg, 0.02 mmol, 10 mol%), 1,1-dibromoalkene **147** (75.0 mg, 0.22 mmol) and 4-acetylphenylboronic acid (38.0 mg, 0.25 mmol) under nitrogen. The resulting solution was stirred for 15 min at room temperature, then freshly prepared aqueous thallium hydroxide solution (0.4 M, 0.55 mL, 0.22 mmol) was added *via* syringe and the mixture was stirred at room temperature for 2 days. The solution was partitioned between water (3 mL) and EtOAc (3 mL), the layers were separated and the aqueous phase was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue (a mixture of starting material, monocoupled product **184** and dicoupled product **185**) was purified by flash chromatography (10% acetone/petrol) yielding in order of elution; recovered dibromoalkene **147** (18.0 mg, 24%);

monobromoalkene **184** (12.4 mg, 16%) as a yellow oil; R_f(petrol:acetone 80:20) 0.20; ν_{max} (neat)/cm^{-1} 3031 (unsaturated CH), 2937 (saturated CH), 1678 (C=O), 1600 (Ar C=C), 1113 (C-O); δ_H (400 MHz, $CDCl_3$) 7.92-7.88 (2H, m, Ar), 7.48-7.46 (2H, m, Ar), 3.894 (2H, s, 1 x CH_2-O), 3.889 (2H, s, 1 x CH_2-O), 2.89-2.80 (1H, m, 1 x H-2 or 1 x H-8), 2.72-2.68 (2H, m, H-3, H-7), 2.60-2.50 (4H, m (including a singlet at 2.59), 1 x H-2 or 1 x H-8, CH_3CO), 2.33-2.28 (1H, m, 1 x H-2 or 1 x H-8), 2.05-1.95 (2H, m, 1 x H-2 or 1 x H-8, 1 x H-4 or 1 x H-6), 1.78-1.69 (2H, m, 1 x H-4 , 1 x H-6), 1.60 (1H, dd, *J* 14.6, 6.1, 1 x H-4 or 1 x H-6); δ_C (100 MHz, $CDCl_3$) 197.4 (C=O), 147.5 (C), 145.1 (C), 136.1 (C), 129.2 (2 x Ar CH), 128.3 (2 x Ar CH), 118.8 (C-5), 112.1 (C), 64.6 (CH_2-O), 63.9 (CH_2-O), 42.9 (CH_2), 42.6 (C-3 or C-7), 42.4 (CH_2), 41.8 (CH_2), 39.9 (C-3 or C-7), 38.9 (CH_2), 26.6 ($\underline{C}H_3CO$); m/z (FAB$^+$) 377.0 (100%, $(M+H)^+$), Found $(M+H)^+$, 378.0713, $C_{19}H_{22}O_3{}^{81}Br$ requires 378.0654 and *diarylalkene* **185** (18.3 mg, 20%) as a yellow oil; R_f(petrol:acetone 80:20) 0.10; ν_{max} (neat)/cm^{-1} 2933 (saturated CH), 1682 (C=O), 1597 (Ar C=C), 1114 (C-O); δ_H (270 MHz, $CDCl_3$) 7.92-7.88 (4H, m, Ar), 7.26-7.23 (4H, m, Ar), 3.90 (4H, s, 2 x CH_2-O), 2.76-2.55 (10H, m (including a singlet at 2.58), 1 x H-2, H-3, H-7, 1 x H-8, 2 x CH_3CO), 2.40-2.32 (2H, m, 1 x H-2, 1 x H-8), 2.02-1.96 (2H, m, 1 x H-4, 1 x H-6), 1.66-1.59 (2H, m, 1 x H-4, 1 x H-6); δ_C (67.5 MHz, $CDCl_3$) 197.6 (2 x C=O), 147.3 (C), 146.1 (C), 135.2 (C), 132.8 (C), 129.5 (4 x Ar CH), 128.3 (4 x Ar CH), 118.6 (C-5), 64.6 (CH_2-O), 63.9 (CH_2-O), 42.0 (CH_2), 40.2 (C-3, C-7), 38.7 (CH_2), 26.6 (2 x $\underline{C}H_3CO$); m/z (EI$^+$) 416.2 (71%, M^+); Found M^+, 416.19879, $C_{27}H_{28}O_4$ requires 416.19876.

The enantiomers of **184** were separated by HPLC using a Chiralcel OD column (90:10 hexanes:*iso*propanol), 1 mL/min; t_r = 11.2 min and t_r = 16.1 min.

Preparation of (3*R,7*S**)-1-(bromo(4-methoxyphenyl)methylene)-3,7-dimethyl-5-(1,3-dioxolan-2-yl)-*cis*-bicyclo[3.3.0]octane (186) and (3*R**,7*S**)-5-(1,3-dioxolan-2-yl)-3,7-dimethyl-1-bis((4-methoxyphenyl)methylene)-*cis*-bicyclo[3.3.0]octane (187)**

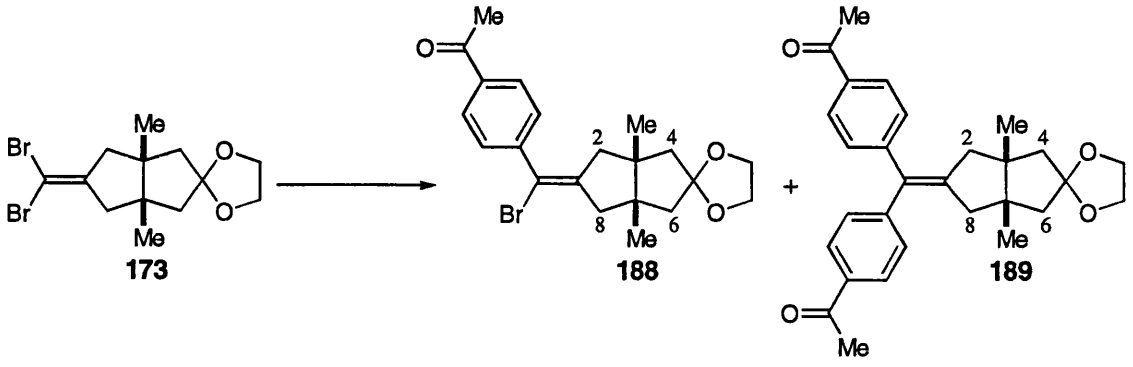


Dry dimethoxyethane (1 mL) was added to a mixture of caesium fluoride (62.1 mg, 0.32 mmol), $Pd(dba)_2$ (26.0 mg, 0.014 mmol, 10 mol%), P(*o*-tolyl)$_3$ (8.3 mg, 0.03 mmol), 1,1-dibromoalkene **173** (50.0 mg, 0.14 mmol) and 4-methoxyphenylboronic acid (26.0 mg, 0.17 mmol). The resulting mixture was heated at 60 °C for 1 day. The solution was partitioned between EtOAc (3 mL) and water (3 mL). The aqueous phase was extracted with EtOAc (2 x 2 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue (a mixture of starting material, monocoupled product **186** and dicoupled product **187**) was purified by flash chromatography (15% EtOAc/petrol) to give in order of elution; recovered dibromide **173** (18.5 mg, 37%); *monobromoalkene* **186** (3.8 mg, 7%) as a yellow oil; R_f(petrol:EtOAc 85:15) 0.36; ν_{max} (neat)/cm^{-1} 3033 (unsaturated CH), 2931 (saturated CH), 2832 (O-CH_3), 1599 (Ar C=C), 1112 (C-O); m/z (FAB$^+$) 394.0 (49%, $(M+H)^+$); Found M^+, 394.0943, $C_{20}H_{25}O_3{}^{81}Br$ requires 394.0966 and *diarylalkene* **187** (9.4 mg, 16%) as a yellow oil, R_f(petrol:EtOAc 85:15) 0.29; ν_{max} (neat)/cm^{-1} 3029 (unsaturated CH), 2936 (saturated CH), 2833 (O-CH_3), 1600 (Ar C=C), 1115 (C-O); δ_H (400 MHz, $CDCl_3$) 7.10-7.07 (4H, m, Ar), 6.84-6.80 (4H, m, Ar), 3.86 (4H, s, 4 x CH_2-O), 3.79

(6H, s, 2 x CH_3O), 2.64 (2H, d, *J* 19.2, H-2a, H-8a), 2.32 (2H, d, *J* 19.2, H-2b, H-8b), 2.05 (2H, d, *J* 14.3, H-4a, H-6a), 1.83 (2H, d, *J* 14.3, H-4b, H-6b), 0.98 (6H, s, 2 x CH_3); δ_C (67.5 MHz, $CDCl_3$) 157.7 (2 x C-OMe), 139.0, 136.0, 132.4 (C), 130.3 (4 x Ar CH), 128.3 (C), 116.9 (C-5), 113.3 (4 x Ar CH), 63.9 (CH_2-O), 63.8 (CH_2-O), 55.2 (2 x CH_3O), 49.6 (CH_2), 45.7 (CH_2), 21.8 (CH_3).

The enantiomers of **186** were separated by HPLC using a Chiralcel OD column (99:1 hexanes:*iso*propanol), 1 mL/min; t_r = 6.8 min and t_r = 7.6 min.

Preparation of (3*R,7*S**)-1-(bromo(4-acetylphenyl)methylene)-5-(1,3-dioxolan-2-yl)-3,7-dimethyl-*cis*-bicyclo[3.3.0]octane (188) and (3*R**,7*S**)-1-bis((4-acetylphenyl) methylene)-5-(1,3-dioxolan-2-yl)-3,7-dimethyl-*cis*-bicyclo[3.3.0]octane (189)**



Dry dimethoxyethane (1 mL) was added to a mixture of caesium fluoride (41.0 mg, 0.27 mmol), $Pd(dba)_2$ (18.2 mg, 0.009 mmol, 10 mol%), dppb (5.1 mg, 0.009 mmol), 1,1-dibromoalkene **173** (32.5 mg, 0.09 mmol) and 4-acetylphenylboronic acid (26.0 mg, 0.17 mmol) under nitrogen. The resulting mixture was heated at 80 °C for 8 h then

cooled to room temperature. The solution was partitioned between EtOAc (3 mL) and water (3 mL). The aqueous phase was extracted with EtOAc (2 x 2 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue (a mixture of starting material, monocoupled product **188** and dicoupled product **189**) was purified by flash chromatography (10% acetone/petrol) to give in order of elution; recovered dibromide **173** (7.5 mg, 23%); *monobromoalkene* **188** (4.6 mg, 13%) as a yellow oil; R_f(petrol:acetone 80:20) 0.45; ν_{max} (neat)/cm^{-1} 3031 (unsaturated CH), 2932 (saturated CH), 1678 (C=O), 1600 (Ar C=C), 1112 (C-O); δ_H (400 MHz, $CDCl_3$) 7.94-7.90 (2H, m, Ar), 7.49-7.33 (2H, m, Ar), 3.86 (2H, s, 1 x CH_2-O), 3.85 (2H, s, 1 x CH_2-O), 2.77 (1H, d, *J* 18.5, 1 x H-2 or 1 x H-8), 2.64-2.55 (4H, m (including a singlet at 2.60), 1 x H-2 or 1 x H-8, CH_3CO), 2.45 (1H, dd, *J* 18.5, 1.7, 1 x H-2 or 1 x H-8), 2.26 (1H, dd, *J* 16.9, 1.7, 1 x H-2 or 1 x H-8), 2.12 (1H, d, *J* 14.3, 1 x H-4 or 1 x H-6), 1.94 (2H, dd, *J* 14.3, 2.5, 1 x H-4, 1 x H-6), 1.83 (1H, d, *J* 14.3, 1 x H-4 or 1 x H-6), 1.06 (3H, s, 1 x CH_3), 0.95 (3H, s, 1 x CH_3); δ_C (67.5 MHz, $CDCl_3$) 197.5 (C=O), 145.3 (C), 145.0 (C), 136.0 (C), 128.2 (2 x Ar CH), 128.1 (2 x Ar CH), 116.7 (C-5), 113.1 (C), 64.0 (CH_2-O), 63.9 (CH_2-O), 51.5 (C-3 or C-7), 50.1 (CH_2), 49.8 (CH_2), 49.3 (CH_2), 49.1 (CH_2), 45.7 (C-3 or C-7), 26.7 ($\underline{C}H_3CO$), 21.9 (CH_3), 21.4 (CH_3); m/z (FAB^+) 405.0 (50%, M^+), Found M^+, 406.1029, $C_{21}H_{25}O_3{}^{81}Br$ requires 406.0967 and *diarylalkene* **189** (9.0 mg, 23%) as a yellow oil; R_f(petrol:acetone 80:20) 0.34; ν_{max} (neat)/cm^{-1} 3032 (unsaturated CH), 2933 (saturated CH), 1676 (C=O), 1598 (Ar C=C), 1113 (C-O); δ_H (270 MHz, $CDCl_3$) 7.92-7.89 (4H, m, Ar), 7.28-7.25 (4H, m, Ar), 3.86 (4H, s, 2 x CH_2-O), 2.72-2.60 (2H, m, H-2a, H-8a), 2.59 (6H, s, 2 x $COCH_3$), 2.39-2.32 (2H, m, H-2b, H-8b), 2.04 (2H, d, *J* 14.3, H-4a, H-6a), 1.86 (2H, d, *J* 14.3, H-4b, H-6b), 1.03 (6H, s, 2 x CH_3); m/z (FAB^+) 445.1 (100%, $(M+H)^+$); Found M^+, 444.2303, $C_{29}H_{32}O_4$ requires 444.2301.

The enantiomers of **188** were separated by HPLC using a Chiralcel OD column (90:10 hexanes:*iso*propanol), 1 mL/min; t_r = 11.9 min and t_r = 15.0 min.

General procedures of Suzuki coupling with chiral catalysts

-Procedure A: Reactions with $Pd(dba)_2$

Dry THF (3 mL) was added under nitrogen to a mixture of $Pd(dba)_2$ (17 mg, 0.03 mmol, 10 mol%), the appropriate chiral ligand **L** (0.03 mmol, 10 mol% (bidentate) or 0.06 mmol, 20 mol% (monodentate)), 1,1-dibromoalkene **147** or **173** (0.3 mmol) and *para*-substituted phenylboronic acid (0.37 mmol). The resulting solution was stirred until the colour became yellow-orange (from 15 to 45 min). Freshly prepared aqueous thallium hydroxide solution (0.4 M, 0.17 mL, 0.3 mmol) was added *via* syringe and the reaction was stirred at room temperature under nitrogen. The reaction was stopped when no further reaction was observed (by tlc). The reaction mixture was partitioned between EtOAc (2 mL) and water (2 mL) and the aqueous phase was extracted with EtOAc (2 x 2 mL). The combined organic phases were dried (Na_2SO_4) filtered and concentrated under reduced pressure. The residue was purified by flash chromatography.

Preparation of 10% aqueous thallium hydroxide solution

CAUTION: Thallium salts are extremely toxic!

Thallium hydroxide was precipitated from an approximately 6 N solution of thallous formate by the addition of approximately 10 N potassium hydroxide solution, free from carbonate. The yellow precipitate was washed with cold water and a nearly saturated aqueous solution was prepared from the wet product, precautions being taken to prevent

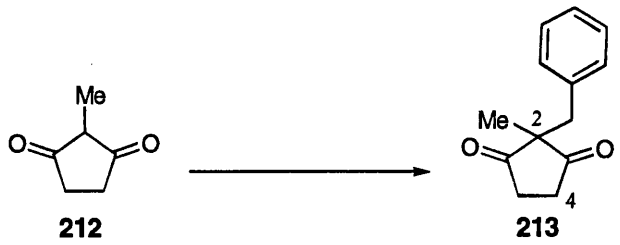
the access of carbon dioxide. The solution was stored at 5 °C and used within one week.

-Procedure B: reactions with $Pd(OAc)_2$

Dry dioxane (3 mL) was added under nitrogen to a mixture of $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 10 mol%), the appropriate chiral ligand **L** (0.03 mmol, 10 mol% (bidentate) or 0.06 mmol, 20 mol% (monodentate)), 1,1-dibromoalkene **147** or **173** (0.3 mmol), *para*-substituted phenylboronic acid (0.37 mmol) and caesium fluoride (136.7 mg, 0.9 mmol). The resulting solution was stirred at room temperature and the reaction was stopped when no further reaction was observed (by tlc). The reaction mixture was partitioned between water (2 mL) and EtOAc (2 mL) and the aqueous phase was extracted with EtOAc (2 x 2 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography.

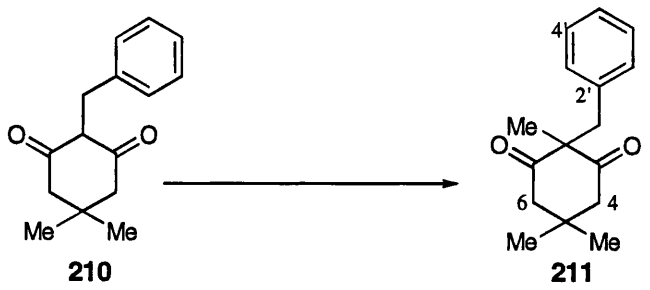
The best enantioselectivity (13% ee) was obtained from the desymmetrisation of dibromide **173** with 4-methoxyphenylboronic acid **180** employing enantiopure ligand *i*-Pr-phosphinoxazoline **104** (Table 18).

Preparation of 2-benzyl-2-methyl-1,3-cyclopentadione (213)



Diketone **212** (1.00 g, 9.0 mmol) was added to a stirred aqueous 1 M sodium hydroxide solution (9 mL, 9.0 mmol). The resulting orange solution was stirred at room temperature for 1 h after which time benzylbromide (1.6 mL, 14.4 mmol) was added dropwise over 1 h. The resulting mixture was stirred for 3 days. The aqueous phase was extracted with DCM (4 x 20 mL), the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (20% ether/petrol) to give the diketone **213** (1.27 g, 70%) as a white solid; data consistent with the literature.[203]

Preparation of 2-benzyl-2,5,5-trimethyl-1,3-cyclohexadione (211)



Iodomethane (0.94 mL, 15.2 mmol) was added *via* syringe to a solution of the diketone **210**[165] (3.00 g, 13.04 mmol) and KI (230 mg, 1.38 mmol) in 1 M *t*-BuOK solution (15.2

mL, in *t*-BuOH). The mixture was gently refluxed for 20 h. The reaction mixture was cooled to room temperature and extracted with ether (4 x 20 mL) and the extracts were washed with 0.5 M sodium hydroxide (30 mL) and water (30 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (25% ether/petrol) to give C-alkylated product **211** (2.65 g, 83%) as a white solid, mp 53-53.5 °C (from hexane); R_f(petrol:EtOAc 66:33) 0.45; ν_{max} (film)/cm^{-1} 3030 (unsaturated CH), 2955 and 2871 (saturated CH), 1726 (C=O), 1496 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.21-7.18 (3H, m, H-4', H-5', H-6'), 7.17-7.03 (2H, m, H-3', H-7'), 3.07 (2H, s, 2 x H-1'), 2.47 (2H, d, *J* 15.0, 1 x H-4, 1 x H-6), 2.35 (2H, d, *J* 15.0, 1 x H-4, 1 x H-6), 1.26 (3H, s, CH_3), 0.87 (3H, s, CH_3), 0.79 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 210.4 (C-1, C-3), 135.9 (Ar C), 130.1, 128.2 and 126.9 (5 x Ar CH), 64.7 (C-2), 52.8 (C-1'), 44.2 (CH_2), 30.2 (C-5), 29.2 (CH_3), 28.2 (CH_3), 20.8 (CH_3); Found C, 78.20; H, 8.28%. $C_{16}H_{20}O_2$ requires C, 78.68; H, 8.20%; data consistent with the literature.[166]

Preparation of the monotriflate and ditriflate compounds

General procedure the synthesis of monotriflates

A solution of trifluoromethanesulfonic anhydride (2.5 mL, 14.7 mmol) in dry DCE (5 mL) was added dropwise under nitrogen to a stirred solution of the diketone (7 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (3.24 g, 15 mmol) in dry DCE (30 mL) at 0 °C. The reaction was heated at 80 °C for 18 h after which time the mixture was cooled to room temperature. Ether was added (150 mL) and the white pyridinium triflate salt was filtered, washed with ether (30 mL) and the filtrate was concentrated under reduced pressure to give a dark orange oil. The residue was purified by flash chromatography.

General procedure for the synthesis of ditriflates

A solution of potassium hexamethyldisilazide (0.5 M in toluene, 19.4-20.2 mL, 9.7-10.1 mmol) was added over 1 h to a stirred mixture of diketone (4.6 mmol) and *N*-5(chloro-2-pyridyl)triflimide (5.90 g, 10.1 mmol) in dry THF (40 mL) at –78 °C. The reaction mixture was stirred at this temperature for 1 h then it was slowly warmed up to room temperature over 3 h. The mixture was diluted with hexane (90 mL), washed with water (50 mL), 10% NaOH (50 mL) and brine (50 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a dark oil which was purified by flash chromatography.

Preparation of 6-benzyl-6-methyl-5-oxo-1-cyclohexen-1-yl trifluoromethane sulfonate (208)

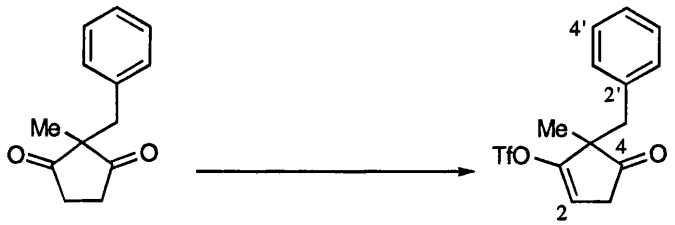
207 **208**

The general procedure for the preparation of monotriflate was followed using trifluoromethanesulfonic anhydride (4.5 mL, 27 mmol), diketone **207** (3.0 g, 14 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (6.3 g, 30 mmol) in dry DCE (80 mL). The residue was purified by flash chromatography (gradient elution, 2-10% EtOAc/petrol) to give *monotriflate* **208** (3.55 g, 73%) as an orange oil; ν_{max} (neat)/cm^{-1} 3065 (unsaturated CH), 2936 (saturated CH), 1722 (C=O), 1680 (C=C), 1416 (O-SO_2), 1142 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.28-7.20 (3H, m, H-4', H-5', H-6'), 7.08-7.02 (2H, m, H-3', H-7'), 5.97

(1H, dd app.t, *J* 4.7, 4.7, H-2), 3.17 (1H, d, *J* 13.5, 1 x H-1'), 2.83 (1H, d, *J* 13.5, 1 x H-1'), 2.40-2.32 (1H, m, 1 x H-4), 2.21-2.12 (1H, m, 1 x H-3), 1.95 (1H, app.dt, *J* 15,2, 6.2, 1 x H-4), 1.74-1.65 (1H, m, 1 x H-3), 1.42 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 209.4 (C-5), 149.6 (C-1), 136.3 (Ar C), 130.1, 128.5 and 128.2 (5 x Ar CH), 118.8 (q, *J* 319, CF_3), 117.9 (C-2), 54.8 (C-6), 43.1 (C-1'), 37.1 (CH_2), 23.4 (CH_3), 19.6 (CH_2); δ_F (376 MHz, $CDCl_3$) –74.91; Found C, 51.5; H, 4.35%. $C_{15}H_{15}O_4SF_3$ requires C, 51.7; H, 4.31%.

The enantiomers of **208** were separated by HPLC using a Chiralcel OD column (99:1 hexanes:*iso*propanol), 0.5 mL/min; t_r = 11.5 min and t_r = 12.4 min.

Preparation of 5-benzyl-5-methyl-4-oxo-1-cyclopenten-1-yl trifluoromethane sulfonate (215)

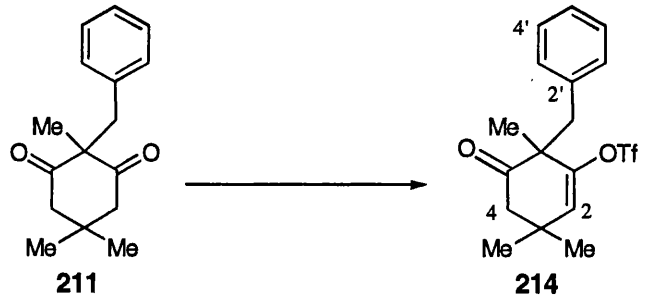


213 **215**

The general procedure for the preparation of monotriflate was followed employing trifluoromethanesulfonic anhydride (2.1 mL, 12.9 mmol), diketone **213** (1.24 g, 6.14 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (2.78 g, 13.5 mmol) in dry DCE (35 mL). The residue was purified by flash chromatography (gradient elution, 0-2% EtOAc/petrol) to give *monotriflate* **215** (1.36 g, 66%) as an orange oil; ν_{max} (neat)/cm^{-1}

3032 (unsaturated CH), 2979 and 2933 (saturated CH), 1761 (C=O), 1649 (C=C), 1427 (O-SO_2), 1140 (SO_2); δ_H (270 MHz, $CDCl_3$) 7.26-7.22 (3H, m, H-4', H-5', H-6'), 7.06-7.03 (2H, m, H-3', H-7'), 5.73 (1H, dd app.t, *J* 2.6, 2.2, H-2), 2.99 (1H, d, *J* 13.4, 1 x H-1'), 2.84 (1H, dd, *J* 22.5, 2.6, 1 x H-3), 2.79 (1H, d, *J* 13.4, 1 x H-1'), 2.27 (1H, dd, *J* 22.5, 2.2, 1 x H-3), 1.31 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 216.3 (C-4), 150.3 (C-1), 135.3 (Ar C), 129.4 , 128.2 and 127.0 (5 x Ar CH), 118.3 (q, *J* 319, CF_3), 110.8 (C-2), 60.4 (C-5), 42.2 (C-1'), 41.5 (C-3), 20.6 (CH_3); Found C, 50.5; H, 3.85%. $C_{14}H_{13}O_4SF_3$ requires C, 50.3; H, 3.89%.

Preparation of 6-benzyl-3,3,6-trimethyl-5-oxo-1-cyclohexen-1-yl trifluoromethane sulfonate (214)



211 **214**

The general procedure for the preparation of monotriflate was followed employing trifluoromethanesulfonic anhydride (0.96 mL, 5.74 mmol), diketone **211** (0.70 g, 2.87 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (1.34 g, 6.31 mmol) in dry DCE (20 mL). The residue was purified by flash chromatography (gradient elution 10-30% DCM/petrol) to give *monotriflate* **214** (0.97 g, 90%) as a bright yellow oil; ν_{max} (neat)/cm^{-1} 3033 (unsaturated CH), 2963 and 2933 (saturated CH), 1724 (C=O), 1675 (C=C), 1416 (O-SO_2), 1212 (O-SO_2), 1142 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.27-7.20 (3H,

m, H-4', H-5', H-6'), 7.19-7.05 (2H, m, H-3', H-7'), 5.81 (1H, s, H-2), 3.09 (1H, d, *J* 13.4, 1 x H-1'), 2.87 (1H, d, *J* 13.4, 1 x H-1'), 2.26 (1H, d, *J* 14.7, 1 x H-4), 1.69 (1H, d, *J* 14.7, 1 x H-4), 1.41 (3H, s, CH_3), 1.02 (3H, s, CH_3), 0.47 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 208.2 (C-5), 147.8 (C-1), 135.9 (Ar C), 130.1, 128.1 and 127.4 (5 x Ar CH), 126.9 (C-2), 118.3 (q, *J* 319, CF_3), 53.7 (C-6), 51.4 (C-1'), 41.8 (CH_2), 32.5 (C-3), 29.5 (CH_3), 28.5 (CH_3), 23.6 (CH_3); m/z (EI^+) 376.1 (100%, M^+); Found $(M+NH_4)^+$, 394.1306, $C_{17}H_{23}O_4SF_3NO_4$ requires 394.1300.

Preparation of 6-benzyl-6-methyl-5-((trifluoromethylsulfonyl)oxy)-1,4-cyclohexa dien-1-yl trifluoromethanesulfonate (209)

207 **209**

The general procedure for the preparation of ditriflate was followed employing KHMDS (0.5 M in toluene, 4.2 mL, 2.1 mmol), diketone **207** (216 mg, 1 mmol) and *N*-5(chloro-2-pyridyl)triflimide (980 mg, 2.3 mmol) in dry THF (20 mL). The residue was purified by flash chromatography (gradient elution, 5-10% ether/petrol) to give in order of elution; *ditriflate* **209** (197 mg, 41%) as a white solid, mp 89.5-90.5 °C (from MeOH); ν_{max} (film)/cm^{-1} 3054 (unsaturated CH), 2987 (saturated CH), 1673 (C=C), 1418 (O-SO_2), 1141 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.29-7.21 (3H, m, H-4', H-5', H-6'), 7.10-7.06 (2H, m, H-3', H-7'), 5.69 (2H, dd app.t, *J* 3.9, 3.5, H-2, H-4), 2.87 (2H, s, 2 x H-1'), 2.76 (1H, dt, *J* 22.8, 3.9, 1 x H-3), 2.33 (1H, dt, *J* 22.8, 3.5, 1 x H-3), 1.55 (3H, s,

CH_3); δ_C (75 MHz, $CDCl_3$) 147.7 (C-1, C-5), 135.0 (Ar C), 130.1, 128.5 and 127.4 (5 x Ar CH), 118.7 (q, *J* 319, 2 x CF_3), 114.2 (C-2, C-4), 45.9 (C-6), 42.1 (C-1'), 24.5 (C-3), 23.1 (CH_3); δ_F (376 MHz, $CDCl_3$) –74.80; m/z (EI^+) 388 (45%, $(M\text{-Bn})^+$); Found C, 40.0; H, 3.00%. $C_{16}H_{14}O_6S_2F_6$ requires C, 40.0; H, 2.92%; monotriflate **208** (53 mg, 16%) and recovered starting material **207** (60.5 mg, 28%) all data consistent with above.

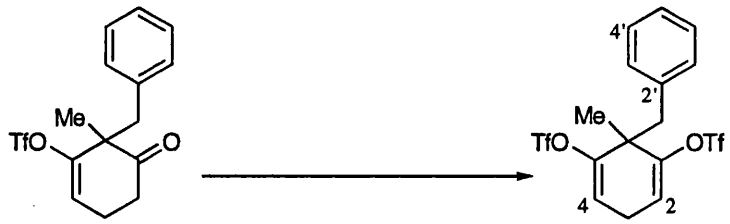
Preparation of 6-benzyl-6-methyl-5-((trifluoromethylsulfonyl)oxy)-1,4-cyclohexa dien-1-yl trifluoromethanesulfonate (209) (modified procedure)

207 **209**

A solution of potassium hexamethyldisilazide (0.5 M in toluene, 1.2 mL, 0.6 mmol) was added over 15 min to a stirred mixture of diketone **207** (108 mg, 0.5 mmol) in dry THF (2 mL) at –78 °C. The reaction mixture was stirred at this temperature for 1 h before a solution of *N*-5(chloro-2-pyridyl)triflimide (235 mg, 0.6 mmol) in dry THF (1 mL + 0.5 mL rinse) was added *via* cannula and the mixture stirred at this temperature for a further hour. A further solution of potassium hexamethyldisilazide (0.5 M in toluene, 1.2 mL, 0.6 mmol) was added over 15 min to the stirred mixture, stirred at -78 °C for 1 h then a solution of *N*-5(chloro-2-pyridyl)triflimide (235 mg, 0.6 mmol) in dry THF (1 mL + 0.5 mL rinse) was added *via* cannula and the mixture stirred at this temperature for a further

hour followed by warm to room temperature over 2 h. The mixture was diluted with hexane (20 mL), washed with water (10 mL), 10% NaOH (10 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a dark oil. The crude product was purified by flash chromatography (gradient elution, 5-10% ether/petrol) to give in order of elution; ditriflate **209** (166 mg, 55%), monotriflate, **208** (22mg, 12%) and recovered diketone **207** (11 mg, 10%); all data consistent with above.

Preparation of 6-benzyl-6-methyl-5-((trifluoromethylsulfonyl)oxy)-1,4-cyclohexa dien-1-yl trifluoromethanesulfonate (209)

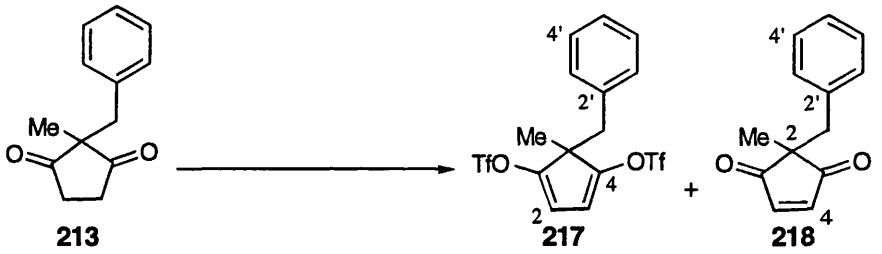


208 **209**

A solution of potassium hexamethyldisilazide (0.5 M in toluene, 1.2 mL, 0.6 mmol) was added over 15 min to a stirred mixture of ketone **208** (174 mg, 0.5 mmol) in dry THF (3 mL) at –78 °C. The resulting orange solution was stirred at this temperature for 1 h after which time a solution of *N*-5(chloro-2-pyridyl)triflimide (235 mg, 0.6 mmol) in THF (1 mL + 0.5 mL rinse) was added *via* cannula and the resulting mixture was stirred at -78 °C for 4 h then warmed to room temperature over 3 h. The mixture was diluted with hexane (20 mL), washed with water (20 mL), 10% NaOH (20 mL) and brine (20

mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a dark oil. The crude product was purified by flash chromatography (gradient elution, 5-10% DCM/petrol) to give the ditriflate **209** (197 mg, 82%); data consistent with above.

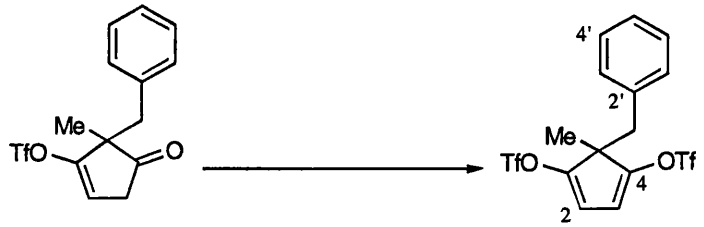
Preparation of 5-benzyl-5-methyl-4-((trifluoromethylsulfonyl)oxy)-1,3-cyclopenta dien-1-yl trifluoromethanesulfonate (217) and 2-benzyl-2-methyl-4-cyclopentene-1,3-dione (218)



The general procedure for the preparation of ditriflate was followed using KHMDS (0.5 M in toluene, 14.5 mL, 7.26 mmol), diketone **213** (0.70 g, 3.46 mmol) and *N*-5(chloro-2-pyridyl)triflimide (2.85 g, 7.26 mmol) in dry THF (28 mL). The residue was purified by flash chromatography (gradient elution 5-30% DCM/petrol) to give in order of elution; *ditriflate* **217** (985 mg, 61%) as a white solid, mp 37-37.5 °C (from MeOH); R_f(petrol:EtOAc 90:10) 0.80; ν_{max} (film)/cm^{-1} 3034 (unsaturated CH), 2982 and 2938 (saturated CH), 1631 (C=C), 1497 (aromatic CH), 1429 (O-SO_2), 1328 (O-SO_2), 1311 (SO_2), 1140 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.25-7.20 (3H, m, H-4', H-5', H-6'), 7.07-7.06 (2H, m, H-3', H-7'), 5.81 (2H, s, H-2, H-3), 2.97 (2H, s, 2 x H-1'), 1.41 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 151.9 (C-1, C-4), 134.0 (Ar C), 128.9, 128.0 and 127.2 (5 x Ar CH), 118.3 (q, *J* 319, 2 x CF_3), 111.9 (C-2, C-3), 54.2 (C-5), 39.7 (C-1'), 18.5

(CH_3); δ_F (376 MHz, $CDCl_3$) –73.80; Found C, 38.4; H, 2.65%. $C_{15}H_{12}O_2S_2F_6$ requires C, 38.6; H, 2.60%; monotriflate **215** (121 mg, 10%), R_f(petrol:EtOAc 90:10) 0.63, data consistent with above and *diketone* **218** (83 mg, 12%) as yellow plates, mp 115-116 °C; R_f(petrol:EtOAc 90:10) 0.36; ν_{max} (film)/cm^{-1} 3055 (unsaturated CH), 2985 and 2931 (saturated CH), 1746 (C=O), 1604 (C=C), 1496 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.18-7.10 (3H, m, H-4', H-5', H-6'), 6.98 (2H, s, H-4, H-5), 6.95-6.90 (2H, m, H-3', H-7'), 2.99 (2H, s, 2 x H-1'), 1.25 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 206.8 (C-1, C-3), 148.5 (C-4, C-5), 135.3 (Ar C), 129.5, 128.1 and 126.8 (5 x Ar CH), 52.0 (C-2), 40.9 (C-1'), 19.3 (CH_3); m/z (EI^+) 200.0 (38%, M^+); Found M^+, 200.0827, $C_{13}H_{12}O_2$ requires 200.0837.

Preparation of 5-benzyl-5-methyl-4-((trifluoromethylsulfonyl)oxy)-1,3-cyclopenta dien-1-yl trifluoromethanesulfonate (217)

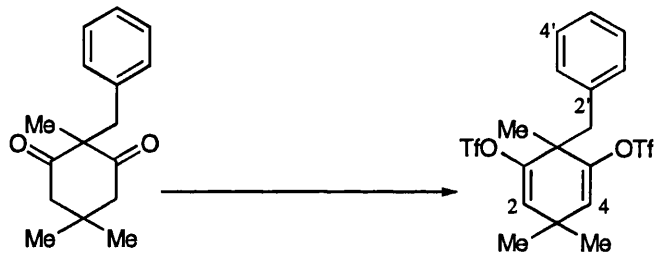


215 **217**

A solution of potassium hexamethyldisilazide (0.5 M in toluene, 1.2 mL, 0.6 mmol) was added over 15 min to a stirred mixture of ketone **215** (167 mg, 0.5 mmol) and *N*-5(chloro-2-pyridyl)triflimide (235 mg, 0.6 mmol) in dry THF (3 mL) at –78 °C. The reaction mixture was stirred at this temperature for 3 h then it was slowly warmed to room temperature over 3 h. The mixture was diluted with hexane (20 mL), washed with

water (20 mL), 10% NaOH (20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a dark oil. The crude product was purified by flash chromatography (gradient elution, 5-10% DCM/petrol) to give the ditriflate **217** (167 mg, 72%); data consistent with above.

Preparation of 6-benzyl-3,3,6-trimethyl-5-((trifluoromethylsulfonyl)oxy)-1,4-cyclo hexadien-1-yl trifluoromethanesulfonate (216)



211 **216**

The general procedure for the preparation of ditriflate was followed using KHMDS (0.5 M in toluene 28.3 mL, 14.1 mmol), diketone **211** (1.50 g, 6.15 mmol) and *N*-5(chloro-2-pyridyl)triflimide (5.54 g, 14.1 mmol) in dry THF (50 mL). The residue was purified by flash chromatography (5% DCM/petrol) to give *ditriflate* **216** (2.86 g, 92%) as a colourless oil which solidified on standing in the fridge (5 °C); ν_{max} (neat)/cm^{-1} 3034 (unsaturated CH), 2968 and 2942 (saturated CH), 1602 (C=C), 1422 (O-SO_2), 1213 (O-SO_2), 1142 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.29-7.18 (3H, m, H-4', H-5', H-6'), 7.06-7.03 (2H, m, H-3', H-7'), 5.48 (2H, s, H-2, H-4), 2.85 (2H, s, 2 x H-1'), 1.52 (3H, s, CH_3), 1.09 (3H, s, CH_3), 0.34 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 145.6 (C-1,C-5), 135.7 (Ar C), 130.1, 128.3 and 127.3 (5 x Ar CH), 124.3 (C-2, C-4), 118.6 (q, *J* 319, 2 x CF_3), 46.1 (C-6), 41.8 (C-1'), 35.5 (C-3), 30.2 (CH_3), 28.7 (CH_3), 23.2 (CH_3); δ_F (376

MHz, $CDCl_3$) –74.70; m/z (EI^+) 508 (100%, M^+); Found $(M+NH_4)^+$, 526.0796, $C_{18}H_{22}NO_6S_2F_6$ requires 526.0793.

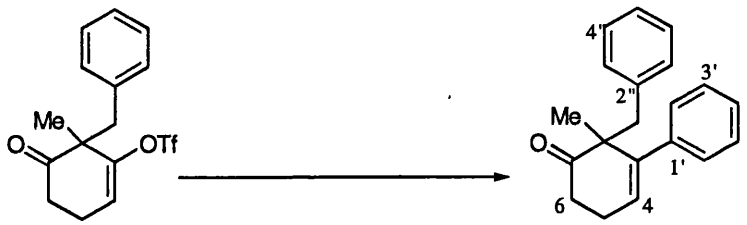
Preparation of 2-benzyl-2-methyl-3-vinyl-3-cyclohexen-1-one (219)

208 **219**

Dry THF (1 mL) was added to a mixture of monotriflate **208** (50.0 mg, 0.15 mmol), $Pd(dba)_2$ (8.1 mg, 0.015 mmol, 10 mol%), tri-furylphosphine (6.7 mg, 0.030 mmol) and LiCl (18.0 mg, 0.50 mmol) and the resulting solution was stirred for 10 min under nitrogen. Tri(butyl)vinyltin (53 μL, 0.017 mmol) was added *via* syringe to the reaction mixture which was stirred for 90 h at room temperature. The mixture was diluted with EtOAc (5 mL), saturated KF solution (2mL) was added and the mixture was stirred for a further hour. The aqueous phase was extracted with EtOAc (2 x 2 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% EtOAc/petrol) to give the *diene* **219** (21.5 mg, 67%) as a yellow oil; ν_{max} (film)/cm^{-1} 3058 (unsaturated CH), 2979 and 2935 (saturated CH), 1708 (C=O), 1616 (C=C); δ_H (400 MHz, $CDCl_3$) 7.20-7.13 (3H, m, H-4", H-5", H-6"), 7.04-7.02 (2H, m, H-3", H-7"), 6.40 (1H, dd, *J* 17.2, 10.9, H-1'), 6.05 (1H, dd app.t, *J* 4.3, 4.3, H-4), 5.50 (1H, dd, *J* 17.2, 1.9, 1 x H-2'), 5.16 (1H, dd, *J* 10.9, 1.9, 1 x H-2'), 3.12 (1H, d, *J* 13.3, 1 x H-1"), 2.84 (1H, d, *J* 13.3, 1 x H-1"), 2.32-2.24 (1H, m, 1 x H-6), 2.19-2.11 (1H, m, 1 x H-5), 1.90 (1H, app.

dt, *J* 14.4, 6.4, 1 x H-6), 1.80-1.71 (1H, m, 1 x H-5), 1.33 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 214.7 (C-1), 141.1 (C-3), 137.9 (Ar C), 135.6 (C-1'), 130.1, 128.1 and 126.6 (5 x Ar CH), 124.8 (C-4), 115.6 (C-2'), 53.1 (C-2), 44.3 (C-1"), 38.0 (CH_2), 25.0 (CH_3), 23.6 (CH_2); m/z (EI^+) 226.2 (45%, M^+); Found M^+, 226.1359, $C_{16}H_{18}O$ requires 226.1358.

Preparation of 2-benzyl-2-methyl-phenyl-3-cyclohexen-1-one (220)

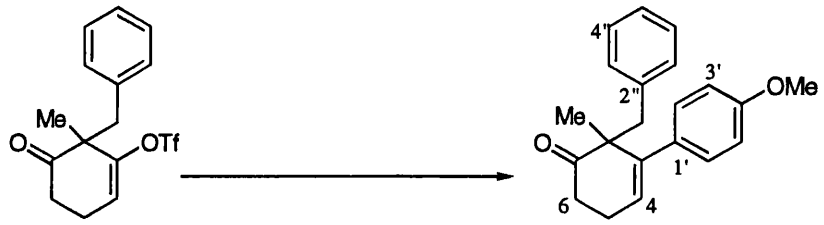


208 **220**

Dry dioxane (1 mL) was added to a mixture of $Pd(PPh_3)_4$, triflate **208** (100.3 mg, 0.29 mmol), phenylboronic acid (49.0 mg, 0.36 mmol), caesium carbonate (187.1 mg, 0.58 mmol) and LiCl (36.5 mg, 0.86 mmol). The mixture was flushed with nitrogen and heated at reflux for 18 h. The reaction was then cooled to room temperature, partitioned between water (4 mL) and EtOAc (4 mL) and the aqueous phase was extracted with EtOAc (2 x 2 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (5% EtOAc/petrol) to give *alkene* **220** (46.0 mg, 58%) as a yellow oil; ν_{max} (film)/cm^{-1} 3082, 3058 and 3028 (unsaturated CH), 2969 and 2930 (saturated CH), 1704 (C=O), 1495 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.36-7.30 (3H, m, Ar), 7.30-7.25 (2H, m, Ar), 7.24-7.19 (3H, m, Ar), 7.08-7.04 (2H, m, Ar), 5.81 (1H, dd app.t, *J*

4.7, 4.3, H-4), 3.14 (1H, d, *J* 13.8, 1 x H-1"), 2.98 (1H, d, *J* 13.8, 1 x H-1"), 2.47-2.43 (2H, m, 2 x H-6), 2.34-2.24 (1H, m, 1 x H-5), 2.00-1.91 (1H, m, 1 x H-5), 1.21 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 214.4 (C-1), 144.6 (C), 141.4 (C), 137.6 (C), 130.2, 129.5, 128.4, 128.1, 128.0 and 127.2 (10 x Ar CH), 126.7 (C-4), 53.8 (C-2), 45.0 (C-1"), 37.6 (CH_2), 24.5 (CH_3), 24.2 (CH_2); m/z (EI^+) 276.2 (22%, M^+); Found M^+, 276.1531, $C_{20}H_{20}O$ requires 276.1542.

Preparation of 2-benzyl-3-(4-methoxyphenyl)-2-methyl-3-cyclohexen-1-one (222)



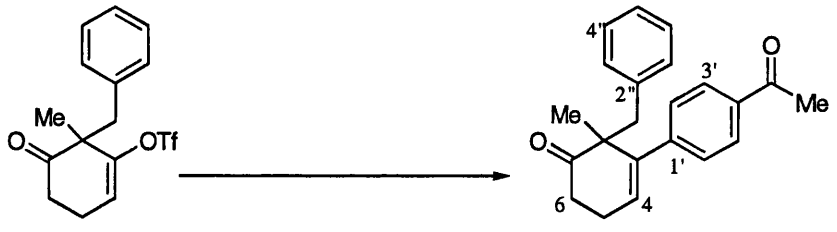
208 **222**

Dry THF (1 mL) was added to a mixture of triflate **208** (50.2 mg, 0.14 mmol), $Pd(OAc)_2$ (3.0 mg, 0.014 mmol, 10 mol%), triphenylphosphine (8.1 mg, 0.032 mmol) and 4-methoxyphenylboronic acid (27.0 mg, 0.18 mmol). The resulting solution was stirred under nitrogen for 10 min then aqueous potassium hydroxide solution (1.78 M, 0.2 mL, 0.1 mmol) was added *via* syringe and the reaction was stirred at room temperature for 40 min. The mixture was partitioned between water (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% DCM/petrol) to give *alkene* **222** (36.0 mg, 82%) as a bright yellow solid; mp 67-68 °C (from DCM/Hexane);

ν_{max} (film)/cm^{-1} 3030 (unsaturated CH), 2932 (saturated CH), 2834 (O-CH_3), 1704 (C=O), 1607 (C=C), 1509 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.24-7.14 (5H, m, Ar), 7.09-7.04 (2H, m, Ar), 6.90-6.85 (2H, m, H-3', H-5'), 5.80 (1H, dd app.t, *J* 3.9, 3.5, H-4), 3.84 (3H, s, OCH_3), 3.14 (1H, d, *J* 13.7, 1 x H-1"), 2.97 (1H, d, *J* 13.7, 1 x H-1"), 2.46-2.43 (2H, m, 2 x H-6), 2.33-2.24 (1H, m, 1 x H-5), 2.02-1.92 (1H, m, 1 x H-5), 1.22 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 214.2 (C-1), 158.4 (C-4'), 143.8 (C), 137.4 (C), 133.5 (C), 130.2, 129.9, 127.9, 127.8 and 126.3 (9 x Ar CH), 113.1 (C-4), 55.3 (C-2), 44.6 (C-1"), 37.3 (CH_2), 24.2 (CH_3), 23.9 (CH_2); m/z (EI$^+$) 306.2 (15%, M^+); Found M^+, 306.1617, $C_{21}H_{22}O_2$ requires 306.1620.

The enantiomers of **222** were separated by HPLC using a Chiralcel OD column (99:1 hexanes:*iso*propanol), 0.5 mL/min; t_r = 18.1 min and t_r = 22.3 min.

Preparation of 3-(4-acetylphenyl)-2-benzyl-2-methyl-3-cyclohexen-1-one (223)

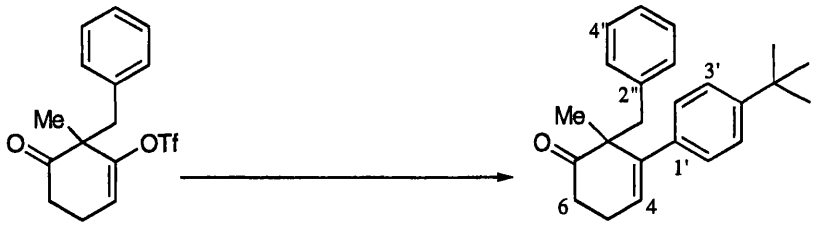


208 **223**

Dry THF (1 mL) was added to a mixture of triflate **208** (50.2 mg, 0.14 mmol), 4-acetylphenylboronic acid (29.5 mg, 0.18 mmol), $Pd(OAc)_2$ (3.0 mg, 0.014 mmol, 10 mol%) and triphenylphosphine (8.1 mg, 0.032 mmol). The solution was stirred for 10 min under nitrogen then aqueous potassium hydroxide solution (1.78 M, 0.1 mL, 0.056 mmol) was added *via* syringe to the mixture. The solution was stirred at room

temperature for 2.5 h. The reaction mixture was partitioned between water (4 mL) and EtOAc (4mL), the aqueous layer separated and extracted with EtOAc (2 x 2 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 2-10% EtOAc/petrol) to give *alkene* **223** (35.6 mg, 78%) as bright orange solid, mp 100-101 °C (from MeOH); ν_{max} (film)/cm^{-1} 3060 and 3031 (unsaturated CH), 2974 (saturated CH), 1703 (C=O), 1676 (C=O), 1603 (C=C), 1496 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.91-7.94 (2H, m, H-3', H-5'), 7.33-7.36 (2H, m, H-2', H-6'), 7.24-7.18 (3H, m, H-4", H-5", H-6"), 7.04-7.01 (2H, m, H-3", H-7"), 5.80 (1H, dd app.t, *J* 3.9, 3.5, H-4), 3.19 (1H, d, *J* 13.7, 1 x H-1"), 2.95 (1H, d, *J* 13.7, 1 x H-1"), 2.63 (3H, s, CH_3CO), 2.49-2.45 (2H, m, 2 x H-6), 2.37-2.30 (1H, m, 1 x H-5), 2.04-1.94 (1H, m, 1 x H-5), 1.23 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 213.4 (C-1), 197.4 (CH_3-<u>C</u>=O), 146.1 (C), 143.5 (C), 137.0 (C), 135.7 (C), 129.8, 129.3, 129.2, 127.9 and 127.8 (9 x Ar CH), 126.5 (C-4), 53.3 (C-2), 44.6 (C-1"), 37.0 (CH_2), 26.7 (<u>C</u>H_3CO), 24.3 (CH_3), 23.8 (CH_2); Found C, 82.2; H, 7.02%. $C_{22}H_{22}O_2$ requires C, 83.0; H, 6.92%.

Preparation of 2-benzyl-3-(4-(*t*-butyl)phenyl)-2-methyl-3-cyclohexen-1-one (224)

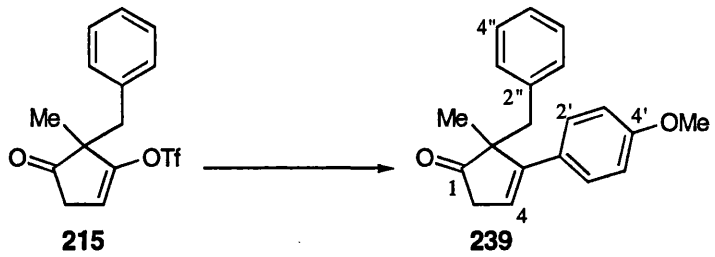


208 **224**

Dry THF (1 mL) was added to a mixture of triflate **208** (50.2 mg, 0.14 mmol), 4-*tert*-butylbenzeneboronic acid (29.5 mg, 0.18 mmol), $Pd(OAc)_2$ (3.0 mg, 0.014 mmol, 10 mol%) and triphenylphosphine (8.1 mg, 0.032 mmol). The solution was stirred for 10 min. under nitrogen then aqueous potassium hydroxide solution (1.78 M, 0.1 mL, 0.056 mmol) was added *via* syringe and the mixture was stirred at room temperature for 2.5 h. The reaction mixture was partitioned between water (4 mL) and EtOAc (4mL), the aqueous layer was extracted with EtOAc (2 x 2 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 2-10% EtOAc/petrol) to give *alkene* **224** (26.6 mg, 58%) as an orange oil; ν_{max} (neat)/cm^{-1} 3060 and 3031 (unsaturated CH), 2974 (saturated CH), 1703 (C=O), 1603 (C=C), 1496 (aromatic CH), 1365 ($C(CH_3)_3$); δ_H (400 MHz, $CDCl_3$) 7.40-7.37 (2H, m, Ar), 7.32-7.28 (2H, m, Ar), 7.24-7.14 (3H, m, Ar), 7.05-7.03 (2H, m, Ar), 5.96 (1H, dd app.t, *J* 4.3, 3.9, H-4), 3.16 (1H, d, *J* 13.7, 1 x H-1"), 2.83 (1H, d, *J* 13.7, 1 x H-1"), 2.39-2.32 (1H, m, 1 x H-6), 2.15 (1H, app.dt, *J*, 15.2, 6.0, 1 x H-5), 1.98-1.91 (1H, m, 1 x H-6), 1.73-1.64 (1H, m, 1 x H-5), 1.41 (3H, s, CH_3), 1.32 (9H, s, $C(CH_3)_3$); δ_C (100 MHz, $CDCl_3$) 214.7 (C-1), 145.0 (C), 144.4 (C), 138.5 (C), 137.8 (C), 130.2, 129.0, 128.2, 128.1 and 126.6 (9 x Ar

CH), 104.6 (C-4), 54.0 (C-2), 45.0 (C-1"), 37.6 (CH_2), 34.9 ($\underline{C}(Me)_3$), 31.8 (CH_3), 24.1 (CH_2).

Preparation of 2-benzyl-3-(4-methoxyphenyl)-2-methyl-3-cyclopenten-1-one (239)

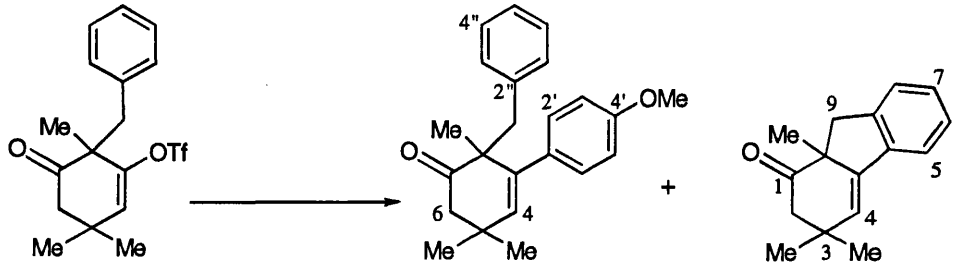


215 **239**

Dry THF (3 mL) was added to a mixture of triflate **215** (100.3 mg, 0.30 mmol), 4-methoxyphenylboronic acid (57.0 mg, 0.37 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 10 mol%) and triphenylphosphine (17.1 mg, 0.07 mmol) and the resulting solution was stirred for 10 min under nitrogen. Aqueous potassium hydroxide solution (1.78 M, 0.2 mL, 0.11 mmol) was added *via* syringe to this solution which was stirred at room temperature for 18 h. The reaction mixture was partitioned between water (8 mL) and EtOAc (8 mL), the aqueous layer was extracted with EtOAc (2 x 4 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 5-10% ether/petrol) to give *alkene* **239** (10.2 mg, 12%) as a pale yellow oil; ν_{max} (film)/cm^{-1} 3030 (unsaturated CH), 2964 and 2930 (saturated CH), 2836 (O-CH_3), 1745 (C=O), 1607 (C=C); δ_H (270 MHz, $CDCl_3$) 7.50-7.45 (2H, m, H-3', H-5'), 7.17-7.07 (3H, m, H-4", H-5", H-6"), 6.98-6.86 (4H, m, H-2', H-6', H-3", H-7"), 6.07 (1H, dd app.t, *J* 2.7, 2.3, H-4), 3.87 (3H, s, OCH_3), 3.09 (1H, d, *J* 13.3, 1 x H-1"), 3.03 (1H, d, *J* 13.3, 1 x H-1"), 2.77 (1H, dd, *J* 22.2, 2.7, 1 x H-5), 2.21 (1H, dd, *J* 22.2 and 2.3, 1 x H-5), 1.48 (3H,

s, CH_3); δ_C (100 MHz, $CDCl_3$); 221.4 (C-1), 159.3 (C-4'), 146.0 (C), 137.3 (C), 130.0 and 129.3 (Ar CH), 128.2 (C), 127.9, 126.6 and 122.1 (Ar CH), 114.2 (C-4), 58.2 (C-2), 55.7 (OCH_3), 44.1 (C-1"), 42.7 (C-5), 23.8 (CH_3); m/z (EI^+) 292.1 (23%, M^+), 91.1 (100%, Bn); Found $(M+H)^+$, 293.1542, $C_{20}H_{21}O_2$ requires 293.1541.

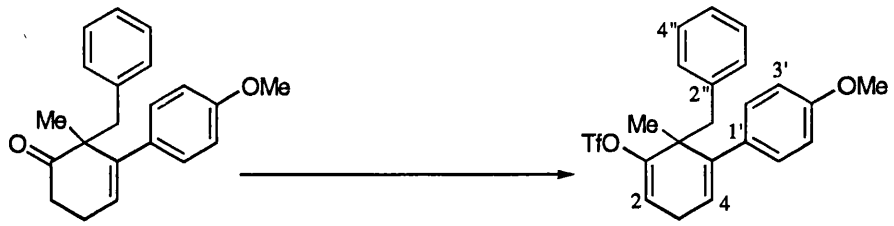
Preparation of 2-benzyl-3-(4-methoxyphenyl)-2,5,5-trimethyl-3-cyclohexen-1-one (225) and 3,3,9a-trimethyl-2,3,9,9a-tetrahydro-1H-fluoren-1-one (226b)



Dry THF (2 mL) was added to a mixture of triflate **214** (75.2 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), triphenylphosphine (11.5 mg, 0.044 mmol) and 4-methoxyphenylboronic acid (38.0 mg, 0.25 mmol) and the resulting solution was stirred under nitrogen for 10 min. Aqueous potassium hydroxide solution (1.78 M, 0.12 mL, 0.2 mmol) was then added *via* syringe and the reaction was stirred at room temperature for 80 min. The mixture was partitioned between water (5 mL) and EtOAc (5 mL), the aqueous layer extracted with EtOAc (2 x 2 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 2-6% ether/petrol) to give in order of elution; *tricyclic alkene* **226b** (8.2 mg, 18%) as a light yellow oil; R_f(petrol:EtOAc 95:5) 0.26; ν_{max} (neat)/cm^{-1} 3018 (unsaturated CH), 2957 (saturated CH), 2864 (O-CH_3), 1715

(C=O); δ_H (400 MHz, $CDCl_3$) 7.43-7.41 (1H, m, Ar), 7.29-7.21 (3H, m, Ar), 5.86 (1H, s, H-4), 3.27 (1H, d, *J* 16.0, 1 x H-9), 2.87 (1H, d, *J* 14.4, 1 x H-2), 2.67 (1H, d, *J* 16.0, 1 x H-9), 2.27 (1H, d, *J* 14.4, 1 x H-2), 1.40 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.10 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 213.0 (C-1), 144.2 (C), 142.0 (C), 138.8 (C), 128.4 (CH), 128.0 (CH), 127.1 (CH), 126.1 (CH), 121.3 (CH), 54.6 (C), 50.4 (CH_2), 39.9 (CH_2), 39.3 (C), 31.7 (CH_3), 31.0 (CH_3), 28.4 (CH_3); m/z (CI^+) 244.2 (100%, M+NH_4^+); Found (M+NH_4)$^+$, 244.1701, $C_{16}H_{22}NO$ requires 244.1701 and *monocyclic alkene* **225** (46.0 mg, 69%) as a bright yellow oil; R_f(petrol:EtOAc 95:5) 0.20; ν_{max} (neat)/cm^{-1} 3030 (unsaturated CH), 2987 and 2966 (saturated CH), 1712 (C=O), 1607 (C=C), 1508 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.27-7.24 (2H, m, Ar), 7.22-7.16 (3H, m, Ar), 7.02-7.00 (2H, m, Ar), 6.91-6.88 (2H, m, H-3', H-5'), 5.58 (1H, s, H-4), 3.04 (1H d, *J* 13.7, 1 x H-1'), 2.89 (1H, d, *J* 13.7, 1 x H-1'), 2.25 (2H, s, 2 x H-6), 1.21 (3H, s, CH_3), 1.00 (3H, s, CH_3), 0.96 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 213.5 (C-1), 159.1 (C-4'), 142.0 (C), 138.8 (Ar CH), 137.7 (C), 133.8 (C), 131.1, 130.5, 128.4 and 126.9 (Ar CH), 113.6 (C-4), 55.7 (OCH_3), 53.1 (C-2), 51.9 (C-5), 45.0 (C-1"), 36.6 (C-6), 30.4 (CH_3), 30.0 (CH_3), 23.7 (CH_3); m/z (EI^+) 334.2 (100%, M^+); Found (M+H)$^+$, 335.2015, $C_{23}H_{27}O_2$ requires 335.2011.

Preparation of 6-benzyl-5-(4-methoxyphenyl)-6-methyl-1,4-cyclohexadien-1-yl trifluoromethane sulfonate (240)



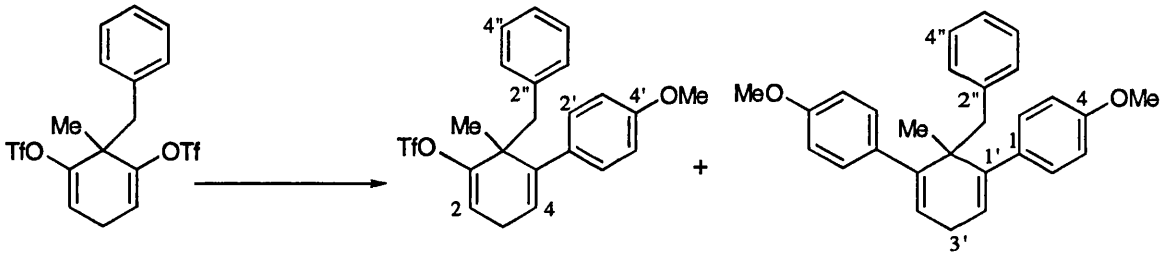
222 **240**

Trifluoromethanesulfonic anhydride (0.28 mL, 1.67 mmol) was added dropwise under nitrogen to a stirred mixture of ketone **222** (161 mg, 0.53 mmol) and 2,6-di-*t*-butyl-4-methylpyridine (270 mg, 1.35 mmol) in dry DCM (3 mL) at 0 °C. The reaction was heated at 40 °C for 18 h and then cooled to room temperature. Ether was added (30 mL) and the white pyridinium triflate salt was filtered off, the residue washed with ether (10 mL) and the filtrate concentrated under reduced pressure to give a dark orange oil. The residue was purified by flash chromatography (gradient elution, 0-2% EtOAc/petrol) to give *triflate* **240** (194 mg, 84%) as an orange oil; ν_{max} (neat)/cm^{-1} 3065 and 3033 (unsaturated CH), 2985 and 2934 (CH saturated), 1611 (C=C), 1418 (O-SO_2), 1178 (O-SO_2), 1140 (SO_2); δ_H (270 MHz, $CDCl_3$) 7.20-7.16 (7H, m, Ar), 6.83-6.79 (2H, m, Ar), 5.63 (1H, dd app.t, *J* 3.1, 2.9, H-2), 5.47 (1H, dd app.t, *J* 4.4, 4.2, H-4), 3.84 (3H, s, CH_3O), 2.90 (1H, d, *J* 14.5, 1 x H-1"), 2.70 (1H, d, *J* 14.5, 1 x H-1"), 2.62 (1H, ddd app.td, *J* 22.9, 4.2, 2.9, 1 x H-3), 2.19 (1H, ddd app.td, *J* 22.9, 4.4, 3.1, 1 x H-3), 1.27 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 158.8 (C-4'), 151.2 (C-1), 141.1 (C), 137.6 (C), 133.1 (C), 130.7, 129.9, 127.7, 126.4 and 125.0 (9 x Ar CH), 118.6 (q, *J* 319, CF_3), 115.0 (C-2 or C-4), 113.2 (C2 or C-4), 55.2 (CH_3O), 44.5 (C-6), 43.1 (C-1"), 26.5 (C-3),

25.25 (CH_3); m/z (EI^+) 347.1 (90%, M^+- CH_2Ph); Found M^+, 347.0523, $C_{15}H_{14}O_4SF_3$ requires 347.0561.

The enantiomers of **240** were separated by HPLC using a Chiralcel OD column (99:1 hexanes:*iso*propanol), 0.5 mL/min; t_r = 11.1 min and t_r = 12.5 min.

Preparation of 6-benzyl-5-(4-methoxyphenyl)-6-methyl-1,4-cyclohexadien-1-yl trifluoromethane sulfonate (240) and 1-(6-benzyl-5-(4-methoxyphenyl)-6-methyl-1,4-cyclohexadien-1-yl)-4-methoxybenzene (241)



209 **240** **241**

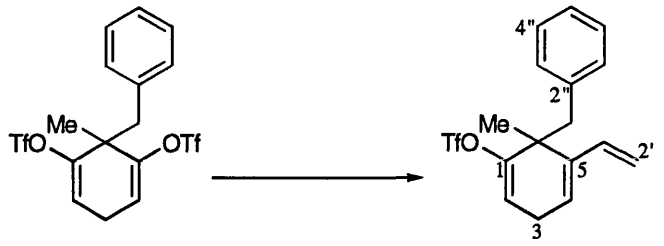
Dry THF (1 mL) was added to a mixture of ditriflate **209** (48.0 mg, 0.1 mmol), 4-methoxyphenylboronic acid (19.0 mg, 0.125 mmol), $Pd(OAc)_2$ (2.1 mg, 0.01 mmol, 10 mol%) and triphenylphosphine (6.0 mg, 0.022 mmol) and the resulting solution was stirred for 10 min under nitrogen. Aqueous potassium hydroxide solution (1.78 M, 0.06 mL, 0.034 mmol) was added *via* syringe and the mixture was stirred at room temperature for 18 h. The reaction mixture was then partitioned between water (3 mL) and EtOAc (3 mL), the aqueous layer extracted with EtOAc (2 x 2 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 10-30%

DCM/petrol) to give in order of elution; recovered starting material **209** (19.2 mg, 40%); *monotriflate* **240** (3.0 mg, 7%), R_f(petrol:DCM 80:20) 0.34; data as given above and *cyclohexadiene* **241** (3.2 mg, 8%) as a white solid; R_f(petrol:DCM 80:20) 0.28; δ_H (270 MHz, $CDCl_3$) 7.52 7.43 (3H, m, H-4", H-5", H-6"), 7.31-7.22 (2H, m, H-3", H-7"), 7.14-7.02 (4H, m, H-3, H-5), 6.84-6.80 (4H, m, H-2, H-6), 5.62 (2H, dd app.t, *J* 4.0, 3.9, H-2', H-4') 3.80 (6H, s, 2 x CH_3O), 2.72 (2H, s, 2 x H-1"), 2.36 (1H, dt, *J* 22.9, 4.0, 1 x H-3'), 2.38 (1H, dt, *J* 22.9, 3.9, 1 x H-3'), 1.17 (3H, s, CH_3); m/z (EI^+) 396.1 (100%, M^+); Found M^+, 396.0781, $C_{28}H_{28}O_2$ requires 396.0786.

General procedure for Stille couplings of ditriflate 209 with achiral catalysts.

Dry solvent (NMP or THF, 2 mL) was added to a mixture of palladium catalyst (0.02 mmol, 10 mol%), ditriflate **209** (96.0 mg, 0.2 mmol) and LiCl (25.4 mg, 0.6 mmol). The resulting solution was stirred for 10 min then the tin reagent (vinyltributyltin, 70 μL or 4-methoxyphenyltributyltin, 92.0 mg dissolved in 1 mL of solvent, 0.25 mmol) was added and the mixture was stirred at the required temperature for the specified time. The solution was diluted with EtOAc (2 mL), saturated KF solution was added (2 mL) and the mixture was stirred for 1 h. The phases were separated, the organic phase was washed with water (2 x 3 mL, if NMP was the solvent employed), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography.

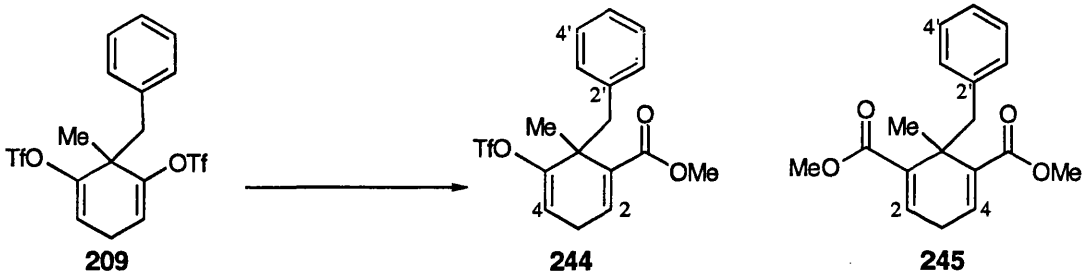
Preparation of 6-Benzyl-6-methyl-5-vinyl-1,4-cyclohaxadien-1-yl trifluoromethane sulfonate (243)



209 **243**

Dry THF (2 mL) was added to a mixture of ditriflate **209** (96.1 mg, 0.2 mmol), $Pd(PPh_3)_4$ (23.0 mg, 0.02 mmol, 10 mol%) and LiCl (25.4 mg, 0.6 mmol) under nitrogen. The resulting solution was stirred for 10 min then vinyltributyltin (70 μL, 0.25 mmol) was added *via* syringe and the resulting mixture was stirred at 70 °C for 8 h. The solution was cooled to room temperature, diluted with EtOAc (2 mL) and saturated KF solution (2 mL) was added. The mixture was stirred for 1 h, the layers were separated and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (gradient elution 0-5% DCM/petrol) to give *triene* **243** (24.0 mg, 32%) as a colourless oil; ν_{max} (neat)/cm^{-1} 3064 and 3031 (unsaturated CH), 2980 and 2929 (CH saturated), 1415 (O-SO_2), 1212 (SO_2), 1178 (O-SO_2), 1144 (SO_2); δ_H (300 MHz, $CDCl_3$) 7.21-7.17 (3H, m, Ar), 7.16-7.05 (2H, m, Ar), 6.44 (1H, dd, *J* 17.1, 10.8, H-1'), 5.74 (1H, dd app.t, *J* 3.6, 3.4, H-4), 5.64 (1H, dd app.t, *J* 4.0, 3.8, H-2), 5.47 (1H, dd, J 17.1, 1.5, 1 x H-2'), 5.19 (1H, dd, J 10.8, 1.5, 1 x H-2'), 2.85 (1H, d, *J* 13.8, 1 x H-1"), 2.81 (1H, d, *J* 13.8, 1 x H-1"), 2.64 (1H, dt, *J* 23.3, 4.0, 1 x H-3), 2.21-2.18 (1H, m, 1 x H-3), 1.45 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 151.0 (C-1), 139.0 (C), 137.6 (C), 135.0, 130.2, 128.0, 126.7 and 121.1 (CH), 118.9 (q, J 319, CF_3), 116.4 (C-2'), 115.0 (CH), 44.3 (C), 43.1 (C-1"), 26.7 (C-3), 24.9 (CH_3); m/z (FAB^+) 266.9 (59%, *M*-CH_2Ph^+).

Preparation of 6-benzyl-6-methyl-1-methoxycarbonyl-5-((trifluoromethylsulfonyl) oxy)-1,4-cyclohexadiene (244) and 2-benzyl-2-methyl-1,3-dimethoxycarbonyl-3,6-cyclohexadiene (245)

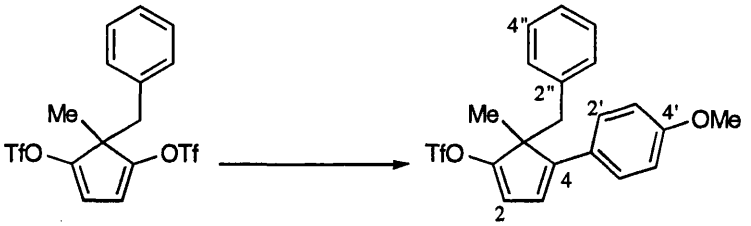


209 244 245

A mixture of ditriflate **209** (144.3 mg, 0.3 mmol), $Pd(OAc)_2$ (2.1 mg, 0.008 mmol, 2.5 mol%), triphenylphosphine (5.0 mg, 0.018 mmol, 6 mol%), triethylamine (85 μL, 0.6 mmol) and MeOH (0.54 mL, 12 mmol) in dry DMF (1.2 mL) was purged with CO for 5 min and stirred for 20 h at room temperature. The mixture was then partitioned between water and ether. The ether layer was washed with water until pH = 7, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 5-10% ether/petrol) to give in order of elution; *monoester* **244** (24.0 mg, 20%) as a colourless oil; R_f(petrol:ether 90:10) 0.33; ν_{max} (neat)/cm^{-1} 3063 and 3030 (unsaturated CH), 2952 and 2884 (saturated CH), 1719 (C=O), 1696 (C=C), 1416 (O-SO_2), 1213 (O-SO_2), 1142 (SO_2); δ_H (270 MHz, $CDCl_3$) 7.19-7.17 (3H, m, H-4', H-5', H-6'), 7.02-6.99 (2H, m, H-3', H-7'), 6.76 (1H, dd app.t *J* 3.5, 3.0, H-2), 5.67 (1H, dd app.t, *J* 4.3, 3.9, H-4), 3.81 (3H, s, CH_3O), 3.51 (1H, d, *J* 13.4, 1 x H-1'), 2.85 (1H, d, *J* 13.4, 1 x H-1'), 2.74 (1H, ddd app.dt, *J* 24.2, 4.3, 3.5, 1 x H-3), 2.28 (1H, ddd app.dt, *J* 24.2, 3.9, 3.0, 1 x H-3), 1.63 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 166.5 (C=O), 151.1 (C), 138.0 (C), 137.2 (C-2), 132.9 (C), 130.2, 128.1 and 126.7 (5 x Ar CH), 118.3 (CF_3), 113.5 (C-4), 52.2 (OCH_3), 43.9 (C-6), 42.2 (C-1'), 26.9

(C-3), 24.3 (CH_3); m/z (FAB^+) 390.9 (20%, $M+H$) $^+$; Found $(M+H)^+$, 390.0732, $C_{17}H_{18}O_5SF_3$ requires 390.0749 and *diester* **245** (9.1 mg, 10%) as a colourless oil; R_f(petrol:EtOAc 90:10) 0.26; ν_{max} (neat)/cm^{-1} 3061 and 3028 (unsaturated CH), 2988 and 2950 (saturated CH), 1720 (C=O); δ_H (270 MHz, $CDCl_3$) 7.17-7.11 (3H, m, H-4', H-5', H-6'), 6.98-6.96 (2H, m, H-3', H-7'), 6.68 (2H, dd app.t, *J* 4.3, 3.0, H-2, H-4), 3.81 (6H, s, 2 x CH_3O), 3.50 (2H, s, 2 x H-1'), 2.58 (1H, dt, *J* 24.6, 4.3, 1 x H-3), 1.99 (1H, dt, *J* 24.6, 3.0, 1 x H-3), 1.58 (3H, s, CH_3); δ_C (300 MHz, $CDCl_3$) 167.8 (2 x C=O), 139.8 (C), 136.1 (C-2, C-4), 135.4 (C), 130.6, 127.7 and 126.1 (5 x Ar CH), 52.0 (2 x OCH_3), 43.1 (C-6), 42.2 (C-1'), 27.5 (C-3), 25.8 (CH_3); m/z (FAB^+) 301.0 (25%, $(M+H)^+$); Found $(M+H)^+$, 301.14399, $C_{18}H_{21}O_4$ requires 301.14398.

Preparation of 5-benzyl-4-(4-methoxyphenyl)-5-methyl-1,3-cyclopentadien-1-yl trifluoromethanesulfonate (246)



217 **246**

Dry THF (2 mL) was added to a mixture of ditriflate **217** (93.2 mg, 0.20 mmol), 4-methoxyphenylboronic acid (38.0 mg, 0.25 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%) and triphenylphosphine (11.5 mg, 0.044 mmol) and the resulting solution was stirred for 10 min under nitrogen. Aqueous potassium hydroxide solution (1.78 M, 0.2 mL, 0.11 mmol) was then added *via* syringe and the mixture was stirred at room

temperature for 1 h. The reaction mixture was partitioned between water (6 mL) and EtOAc (6 mL), the aqueous layer was extracted with EtOAc (2 x 3 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 1-2% EtOAc/petrol) to give *monotriflate* **246** (53.4 mg, 70%) as a solid which decomposes upon exposure to air; ν_{max} (film)/cm^{-1} 3032 (unsaturated CH), 2935 (saturated CH), 2839 (O-CH_3), 1606 (C=C), 1508 (aromatic CH), 1424 (O-SO_2), 1141 (SO_2), 1116 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.56-7.48 (2H, m, Ar), 7.12-7.05 (3H, m, Ar), 6.97-6.94 (2H, m, Ar), 6.85-6.83 (2H, m, Ar), 6.28 (1H, d, *J* 2.8, H-3), 5.95 (1H, d, *J* 2.8, H-2), 3.86 (3H, s, OCH_3), 3.24 (1H, d, *J* 13.7, 1 x H-1"), 3.04 (1H, d, *J* 13.7, 1 x H-1"), 1.62 (3H, s, CH_3).

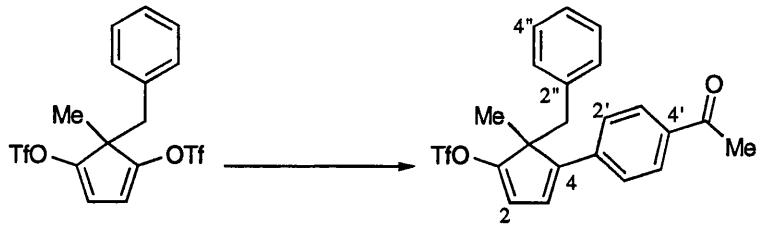
Preparation of 1-(5-benzyl-5-methyl-1,3-cyclopentadien-1-yl)-4-methoxybenzene (248)

246 **248**

Formic acid (2 µL, 0.05 mmol) was added *via* syringe to a stirred mixture of triflate **246** (11.0 mg, 0.025 mmol), tri-*n*-butylamine (20 µL, 0.075 mmol), $Pd(OAc)_2$ (0.6 mg, 0.003 mmol, 10 mol%) and triphenylphosphine (1.4 mg, 0.006 mmol) in dry DMF (0.5 mL). The mixture was stirred at 60 °C for 1 h under argon. EtOAc (2 mL) and water (1 mL) were added and the organic layer was separated, washed with water (3 x 1 mL),

dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% DCM/petrol) in a Pasteur pipette to give *cyclopentadiene* **248** (5.2 mg, 75%) as a yellow solid; ν_{max} (film)/cm^{-1} 3030 (unsaturated CH), 2957 and 2925 (saturated CH) 2850 (O-CH_3), 1606 (C=C), 1503 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.54-7.49 (2H, m, Ar), 7.15-7.11 (3H, m, Ar), 7.01-6.98 (2H, m, Ar), 6.97-6.92 (2H, m, Ar), 6.46 (1H, dd, *J* 2.3, 1.6, :CH), 6.29 (1H, dd, *J* 5.5, 1.6, :CH), 6.21 (1H, dd, *J* 5.5, 2.3, :CH), 3.85 (3H, s, CH_3O), 3.07 (1H, d, *J* 13.1, 1 x H-1"), 2.90 (1H, d, *J* 13.1, 1 x H-1"), 1.38 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 158.7 (C), 152.9 (C), 146.1 (Ar CH), 138.8 (C), 130.2 (CH), 129.4 (C), 128.5, 127.9, 127.7, 126.4, 126.5 and 114.2 (CH), 57.5 (C-1"), 55.7 (CH_3O), 43.5 (C-5'), 21.8 (CH_3); m/z (EI^+) 276.1 (50%, M^+); Found M^+, 276.1503, $C_{20}H_{20}O$ requires 276.1514.

Preparation of 4-(4-acetylphenyl)-5-benzyl-5-methyl-1,3-cyclopentadien-1-yl tri fluoromethanesulfonate (247)



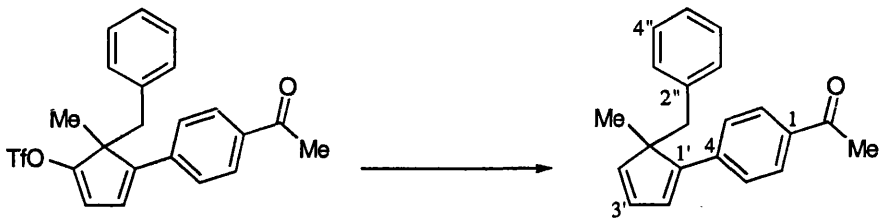
217 **247**

Dry THF (2 mL) was added to a mixture of ditriflate **217** (93.1 mg, 0.20 mmol), 4-acetylphenylboronic acid (41.0 mg, 0.25 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%) and triphenylphosphine (11.5 mg, 0.044 mmol) and the resulting solution was stirred for 10 min under nitrogen. Aqueous potassium hydroxide solution (1.78 M, 0.2 mL, 0.11 mmol) was added *via* syringe and the mixture was stirred at room temperature

for 1 h. The reaction mixture was partitioned between water (6 mL) and EtOAc (6 mL), the aqueous layer was extracted with EtOAc (2 x 3 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 5-10% EtOAc/petrol) to give the *monotriflate* **247** (51.2 mg, 59%) as an orange solid; mp 108.5-109 °C (from MeOH); ν_{max} (film)/cm^{-1} 3033 (unsaturated CH), 2936 and 2840 (saturated CH), 1674 (C=O), 1600 (C=C), 1427 (O-SO_2), 1138 (SO_2); δ_H (270 MHz, $CDCl_3$) 8.02-7.99 (2H, m, H-3', H-5'), 7.66-7.63 (2H, m, Ar), 7.11-7.03 (3H, m, H-4", H-5", H-6"), 6.81-6.77 (2H, m, Ar), 6.59 (1H, d, *J* 3.0, H-3), 6.03 (1H, d, *J* 3.0, H-2), 3.29 (1H, d, *J* 13.8, 1 x H-1"), 3.09 (1H, d, *J* 13.8, 1 x H-1"), 2.64 (3H, s, CH_3C=O), 1.61 (3H, s, CH_3), δ_C (100 MHz, $CDCl_3$) 197.8 (C=O), 159.8 (C), 145.3 (C), 139.5 (C), 136.0 (C), 135.6 (C), 129.3, 128.0, 127.2 and 126.0 (9 x Ar CH), 118.9 (q, J 319, CF_3), 114.1 (C-3), 56.4 (C-1"), 41.5 (C-5), 27.0 ($\underline{C}H_3CO$), 21.6 (CH_3); m/z (EI^+) 436.1 (100%, M^+); Found $(M+H)^+$, 437.1039, $C_{22}H_{20}O_4SF_3$ requires 437.1034.

The enantiomers of **247** were separated by HPLC using a Chiralcel OD column (97:3 hexanes:*iso*propanol), 0.8 mL/min; t_r = 11.7 min and t_r = 14.8 min.

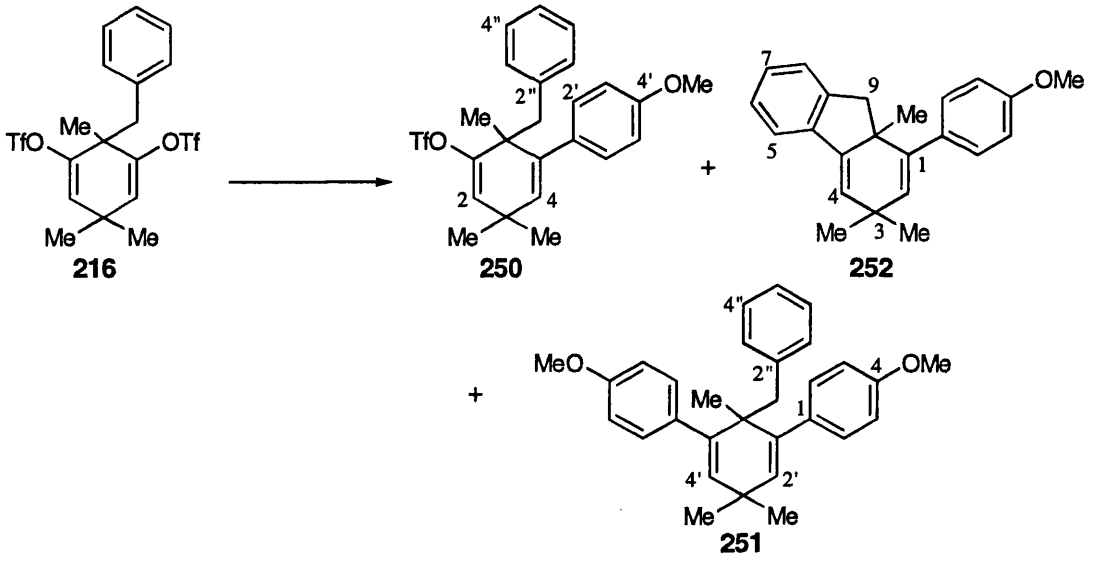
Preparation of 1-(4-(5-benzyl-5-methyl-1,3-cyclopentadien-1-yl)phenyl)-1-ethanone (249)



247 **249**

Formic acid (15 μL, 0.37 mmol) was added *via* syringe to a stirred mixture of vinyltriflate **217** (82.1 mg, 0.19 mmol), tri-*n*-butylamine (0.13 mL, 0.55 mmol), $Pd(OAc)_2$ (2.1 mg, 0.009 mmol, 5 mol%) and triphenylphosphine (5.1 mg, 0.019 mmol) in dry DMF (1.5 mL). The mixture was stirred at 60 °C for 1 h under argon. EtOAc (4 mL) and water (2 mL) were added and the organic layer was separated, washed with water (3 x 3 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% DCM/petrol) to give *cyclopentadiene* **249** (47.0 mg, 87%) as a bright yellow oil; ν_{max} (film)/$cm^{-1}$$\nu_{max}$ (film)/cm^{-1} 3031 (unsaturated CH), 2964 and 2925 (saturated CH), 1678 (C=O), 1600 (C=C); δ_H (400 MHz, $CDCl_3$) 8.00-7.97 (2H, m, H-2, H-6), 7.69-7.66 (2H, m, H-3, H-5), 7.13-7.11 (3H, m, H-3", H-4", H-5"), 6.95-6.92 (2H, m, H-2", H-6"), 6.75 (1H, dd, *J* 2.3, 1.6, :CH), 6.45 (1H, dd, *J* 5.5, 1.6, :CH), 6.25 (1H, dd, J 5.5, 2.3, :CH), 3.12 (1H, d, *J* 13.2, 1 x H-1"), 2.99 (1H, d, *J* 13.2, 1 x H-1"), 2.63 (3H, s, CH_3C=O), 1.45 (3H, s, CH_3), δ_C (75 MHz, $CDCl_3$) 198.1 (C=O), 151.7 (C), 149.0 (CH), 140.8 (C), 138.2 (C), 135.2 (C), 131.0, 130.1, 129.1, 128.6, 127.7, 126.6 and 126.3 (CH), 57.8 (C-1"), 43.3 (C-5'), 26.9 ($\underline{C}H_3CO$), 21.8 (CH_3); m/z (EI^+) 288.1 (50%, M^+); Found M^+, 288.1504, $C_{20}H_{22}O$ requires 288.1514.

Preparation of 6-benzyl-5-(4-methoxyphenyl)-3,3,6-trimethyl-1,4-cyclohexadien-1-yl trifluoromethanesulfonate (250), 1-(6-benzyl-5-(4-methoxyphenyl)-3,3,6-tri methyl-1,4-cyclohexadien-1-yl)-4-methoxybenzene (251) and 1-(4-methoxyphenyl)-3,3,9a-trimethyl-9,9a-dihydro-3H-fluorene (252)

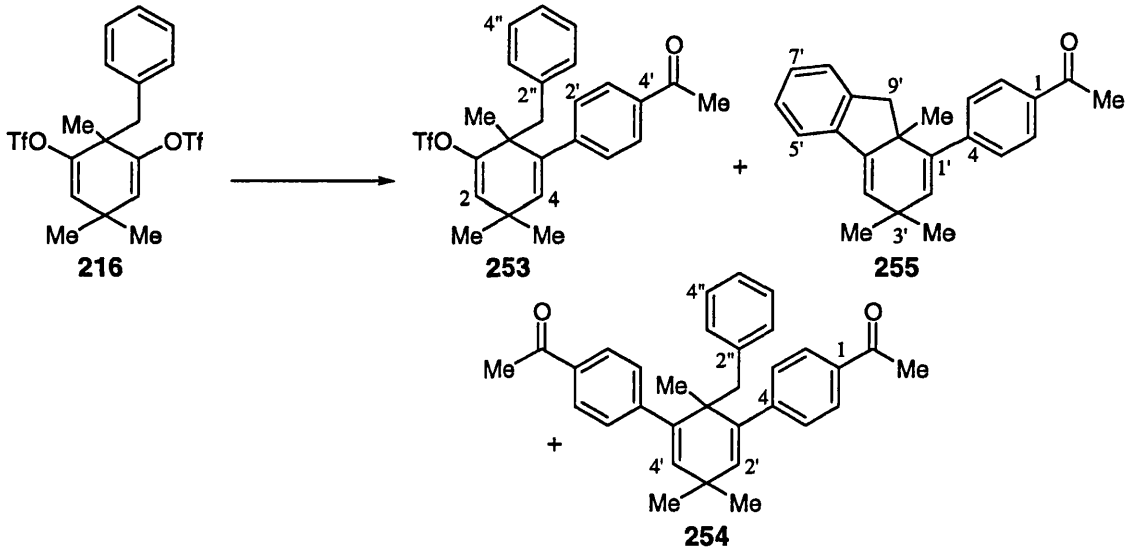


Dry THF (2 mL) was added to a mixture of ditriflate **216** (102.2 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), triphenylphosphine (11.5 mg, 0.044 mmol) and 4-methoxyphenylboronic acid (38.0 mg, 0.25 mmol) under nitrogen and the resulting solution was stirred for 10 min. Aqueous potassium hydroxide solution (1.78 M, 0.4 mL, 0.2 mmol) was added *via* a syringe and the reaction was stirred at room temperature for a further 2.5 h. The mixture was partitioned between water (5 mL) and EtOAc (5 mL), the aqueous layer was extracted with EtOAc (2 x 2 mL) and the combined organic phases dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (1% ether/petrol) to give in order of elution; *tricyclic diene* **252** (16.0 mg, 25%); R_f(petrol:EtOAc 95:5) 0.50; ν_{max} (neat)/cm^{-1} 3001 (unsaturated CH), 2959 (saturated CH), 2860 (O-CH_3), 1607 (C=C),

1510 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.47-7.45 (1H, m, Ar), 7.35-7.33 (2H, m, Ar), 7.28-7.14 (3H, m, Ar), 6.89-6.87 (2H, m, Ar), 5.97 (1H, d, *J* 1.6, H-4), 5.61 (1H, d, *J* 1.6, H-2), 3.83 (3H, s, OCH_3), 2.97 (1H, d, *J* 15.2, 1 x H-9), 2.72 (1H, d, *J* 15.2, 1 x H-9), 1.39 (3H, s, CH_3), 1.28 (1H, s, CH_3), 1.22 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 158.9 (C-OMe), 146.8 (C), 142.9 (C), 142.3 (C), 139.8 (C), 135.6 (CH), 134.9 (C), 129.6 (CH), 128.2 (CH), 128.0 (CH), 127.1 (CH), 127.0 (CH), 126.0 (CH), 121.2 (CH), 113.7 (CH), 55.7 (CH_3O), 47.6 (C), 44.4 (CH_2), 36.8 (C), 31.3 (CH_3), 30.8 (CH_3), 29.9 (CH_3); m/z (EI^+) 316.2 (25%, M^+); Found: $(M+H)^+$, 317.1900, $C_{23}H_{25}O$ requires 317.1905; *monotriflate* **250** (17.1 mg, 18%) as a colourless oil; R_f(petrol:EtOAc 95:5) 0.42; ν_{max} (neat)/cm^{-1} 3032 (unsaturated CH), 2959 and 2936 (saturated CH), 2862 (O-CH_3), 1608 (C=C), 1511 (aromatic CH), 1414 (O-SO_2), 1212 (O-SO_2), 1142 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.31-7.18 (7H, m, Ar), 6.91-6.88 (2H, m, H-3', H-5'), 5.53 (1H, d, *J* 1.7, H-2), 5.32 (1H, d, *J* 1.7, H-4), 3.84 (3H, s, CH_3O), 2.93 (1H, d, *J* 14.3, 1 x H-1'), 2.78 (1H, d, *J* 14.3, 1 x H-1'), 1.38 (3H, s, CH_3), 1.08 (3H, s, CH_3), 0.52 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 158.6 (C-OMe), 149.7 (C-1), 137.4 (2 x C), 135.9 (CH), 132.8 (C), 130.9 (CH), 127.7 (CH), 126.5 (CH), 124.4 (CH), 118.3 (q, *J* 319, CF_3), 113.2 (CH), 53.3 (CH_3O), 45.0 (C-6), 42.6 (C-1"), 35.7 (C-3), 30.7 (CH_3), 28.5 (CH_3), 25.9 (CH_3); m/z (EI^+) 466.1 (100%, M^+); Found: $(M+NH_4)^+$, 484.1774, $C_{24}H_{29}NO_4SF_3$ requires 484.1769 and *diaryldiene* **251** (10.5 mg, 12%) as a pale yellow oil; R_f(petrol:EtOAc 95:5) 0.36; ν_{max} (neat)/cm^{-1} 3030 (unsaturated CH), 2956 and 2928 (saturated CH), 1607 (C=C), 1509 (aromatic CH); δ_H (400 MHz, $CDCl_3$) 7.49-7.43 (2H, m, Ar), 7.28-7.18 (3H, m, Ar), 7.05-6.99 (4H, m, Ar), 6.76-6.72 (4H, m, Ar), 5.43 (2H, s, H-2', H-4'), 3.78 (6H, s, 2 x CH_3O), 2.71 (2H, s, 2 x H-1"), 1.28 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.07 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 158.0 (2 x C-OMe), 140.9 (C), 140.4 (C), 135.9 (CH), 134.6 (C), 130.7, 129.5, 127.6 and 125.5 (Ar CH), 112.6 (C-2',

C-4'), 55.2 (2 x CH_3O), 42.7 (C-6'), 41.7 (C-1"), 34.2 (C-3'), 31.5 (CH_3), 28.8 (CH_3), 30.0 (CH_3); m/z (EI^+) 424.2 (100%, M^+); Found: $(M+H)^+$, 425.2480, $C_{30}H_{33}O_2$ requires M, 425.2480.

Preparation of 5-(4-acetylphenyl)-6-benzyl-3,3,6-trimethyl-1,4-cyclohexadien-1-yl trifluoromethanesulfonate (253), 1-(4-(5-(4-acetylphenyl)-6-benzyl-3,3,6-trimethyl-1,4-cyclohexadien-1-yl)phenyl)-1-ethanone (254) and 1-(4-(3,3,9a-trimethyl-9,9a-dihydro-3H-fluoren-1-yl)phenyl-1-ethanone (255)

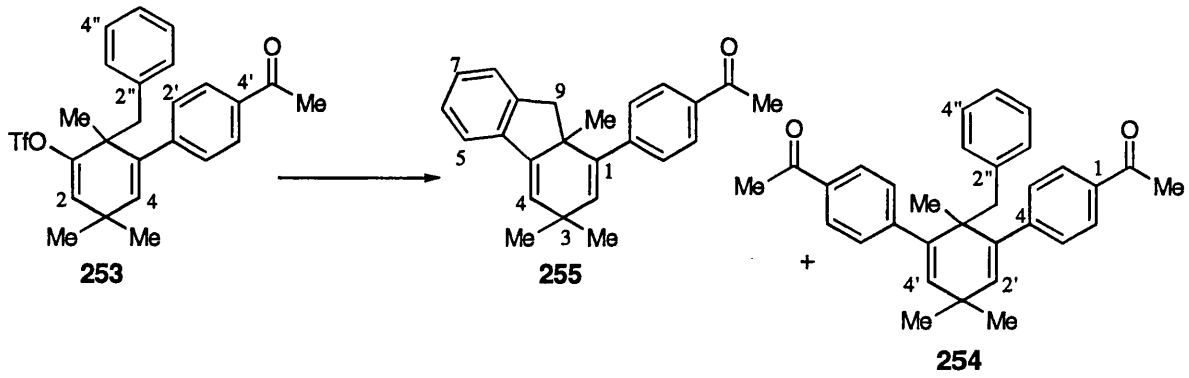


Dry THF (2 mL) was added to a mixture of ditriflate **216** (101.3 mg, 0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%), triphenylphosphine (11.5 mg, 0.044 mmol) and 4-acetylphenylboronic acid (41.0 mg, 0.25 mmol) and the resulting solution was stirred under nitrogen for 10 min. Aqueous potassium hydroxide solution (1.78 M, 0.4 mL, 0.2 mmol) was added *via* syringe and the reaction was stirred at room temperature for 5 h. The mixture was partitioned between water (5 mL) and EtOAc (5 mL), the

aqueous layer extracted (2 x 2 mL EtOAc) and the combined organic phases dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (2% EtOAc/petrol) to give in order of elution; *tricyclic diene* **255** (16.0 mg, 25%) as a colourless oil; R_f(petrol:EtOAc 95:5) 0.39; ν_{max} (neat)/cm^{-1} 3030 (unsaturated CH), 2959, 2925 and 2857 (saturated CH), 1682 (C=O), 1603 (C=C); δ_H (400 MHz, $CDCl_3$) 7.95-7.93 (2H, m, Ar), 7.53-7.47 (3H, m, Ar), 7.24-7.17 (3H, m, Ar), 5.98 (1H, d, *J* 1.6, H-4'), 5.76 (1H, d, *J* 1.6, H-2'), 2.94 (1H, d, *J* 14.8, 1 x H-9'), 2.71 (1H, d, *J* 14.8, 1 x H-9'), 2.64 (3H, s, CH_3C=O), 1.43 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.26 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 197.5 (C=O), 146.7 (C), 146.0 (C), 142.0 (C), 141.7 (C), 138.9 (C), 137.3 (CH), 135.4 (C), 128.1, 128.0, 127.7, 126.7,125.5, 125.3 and 120.7 (CH), 46.9 (C), 43.9 (CH_2), 36.6 (C), 30.9 (CH_3), 30.7 (CH_3), 29.4 (CH_3), 26.7 ($\underline{C}H_3C$=O), m/z (CI^+) 329.3 (100%, M+H^+); Found M^+, 328.1825, $C_{24}H_{24}O$ requires 328.1827; *monotriflate* **253** (16.1 mg, 25%) as a colourless oil; R_f(petrol:EtOAc 95:5) 0.32; ν_{max} (neat)/cm^{-1} 3032 (unsaturated CH), 2963, 2930 and 2860 (saturated CH),1685 (C=O), 1603 (C=C), 1415 (O-SO_2), 1212 (O-SO_2), 1143 (SO_2); δ_H (400 MHz, $CDCl_3$) 7.97-7.95 (2H, m, H-3', H-5'), 7.48-7.46 (2H, m, Ar), 7.29-7.20 (5H, m, Ar), 5.57 (1H, d, *J* 1.7, H-2), 5.38 (1H, d, *J* 1.7, H-4), 2.89 (1H, d, *J* 14.4, 1 x H-1"), 2.83 (1H, d, *J* 14.4, 1 x H-1"), 2.64 (3H, s, CH_3C=O), 1.40 (3H, s, CH_3), 1.11 (3H, s, CH_3), 0.54 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 197.4 (C=O), 149.2 (C), 145.5 (C), 137.4 (C), 137.0 (CH), 136.8 (C), 135.9 (C), 130.0, 127.8, 126.7, 124.5 (6 x CH), 118.7 (q, *J* 319, CF_3), 46.9 (C-1"), 43.9 (C-6), 36.6 (C-3), 30.9 (CH_3), 30.7 (CH_3), 29.4 (CH_3), 26.7 (CH_3); δ_F (376 MHz, $CDCl_3$) –75.09; m/z (EI^+) 478.1 (100%, M^+); Found $(M+H)^+$, 479.1506, $C_{25}H_{27}O_4SF_3$ requires 479.1504 and *diaryldiene* **254** (8.5 mg, 10%) as a light yellow oil; R_f(petrol:EtOAc 95:5) 0.18; δ_H (400 MHz, $CDCl_3$) 7.81-7.79 (4H, m, Ar), 7.42-7.40 (2H, m, Ar), 7.24-7.31 (3H, m, Ar), 7.17-7.15 (4H, m,

Ar), 5.49 (2H, s, H-2', H-4'), 2.70 (2H, s, 2 x H-1''), 2.58 (6H, s, 2 x CH_3C=O), 1.33 (3H, s, CH_3), 1.13 (3H, s, CH_3), 0.54 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 197.7 (2 x C=O), 147.0 (C), 140.6 (C), 139.5 (C), 138.9 (C), 135.4 (CH), 129.9 (CH), 129.3 (CH), 127.8 (CH), 127.4 (CH), 126.0 (CH), 42.3 (C-6'), 41.9 (C-1''), 34.3 (C-3'), 31.3 (CH_3), 30.1 (CH_3), 28.6 (CH_3), 26.7 (CH_3); m/z (EI^+) 448.1 (100%, M^+).

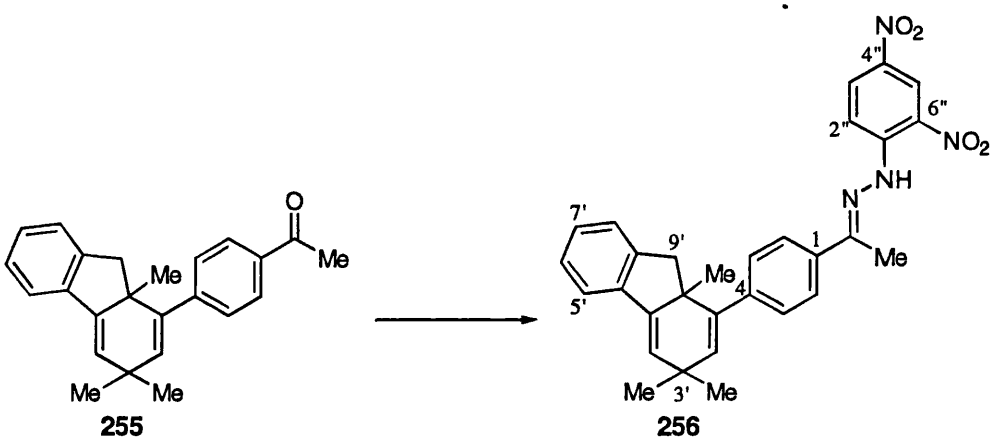
Preparation of 1-(4-(5-(4-acetylphenyl)-6-benzyl-3,3,6-trimethyl-1,4-cyclohexadien-1-yl)phenyl)-1-ethanone (254) and 1(4-(3,3,9a-trimethyl-9,9a-dihydro-3H-fluoren-1-yl)phenyl-1-ethanone (255)



Dry THF (1.2 mL) was added to a mixture of monotriflate **253** (57.0 mg, 0.12 mmol), $Pd(OAc)_2$ (2.7 mg, 0.012 mmol, 10 mol%), triphenylphosphine (7.0 mg, 0.026 mmol) and 4-acetylphenylboronic acid (24.5 mg, 0.15 mmol) and the resulting solution was stirred under nitrogen for 10 min. Aqueous potassium hydroxide solution (1.78 M, 0.09 mL, 0.12 mmol) was added *via* syringe and the reaction was stirred at room temperature for 5 h. The mixture was partitioned between water (3 mL) and EtOAc (3 mL), the aqueous layer extracted (2 x 2 mL EtOAc) and the combined organic phases dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified

by flash chromatography (2% EtOAc/petrol) to give in order of elution tricyclic compound **255** (10 mg, 24%), recovered starting material **253** (5 mg, 6%) and the dicoupled product **254** (40 mg, 65%), all data consistent with above.

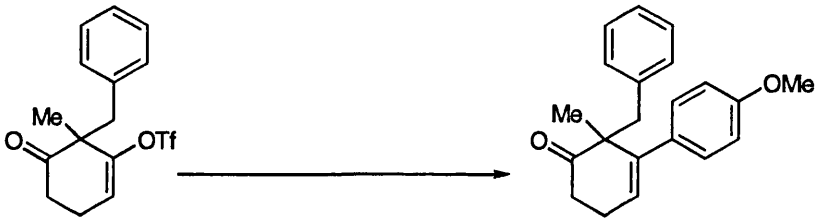
Preparation of 1-(4-(3,3,9a-trimethyl-9,9a-dihydro-3H-fluoren-1-yl)phenyl-1-ethanone *N*-(2,4-dinitrophenyl)hydrazone (256)



Concentrated sulphuric acid (0.14 mL) was added to a stirred solution of ketone **255** (60 mg, 0.18 mmol) in methanol (0.5 mL), then a solution of DNPH (53 mg, 0.27 mmol) in methanol (3mL) was added. An orange precipitate was formed immediately which was filtered, washed with 5% aqueous sodium bicarbonate (1 mL) and water (1 mL) to give the crude hydrazone which was recrystallised from ethanol to give the pure *hydrazone* **256** (88 mg, 95%) as orange crystals, mp 201-203 °C; ν_{max} (film)/cm^{-1} 3315 (NH), 3020 (unsaturated CH), 2960, 2916 and 2850 (saturated CH), 1616 (C=C), 1595 (C-N=O), 1518 (C-NO_2), 1334 (C-NO_2); δ_H (400 MHz, $CDCl_3$) 11.58 (1H, s, NH), 9.17 (1H, d, *J* 2.5, H-5"), 8.37 (1H, dd, *J* 9.6, 2.5, H-3"), 8.15 (1H, d, *J* 9.6, H-2"), 7.85 (2H, d, *J* 8.4, H-2, H-6), 7.53-7.58 (3H, m, Ar), 7.24-7.20 (3H, m, Ar), 6.00 (1H, d, *J* 1.4, H-2' or H-4'), 5.77 (1H, d, *J* 1.4, H-2' or H-4'), 2.98 (1H, d, *J* 15.2, 1 x H-9'), 2.88 (1H, d, *J* 15.2, 1

x H-9'), 2.49 (3H, s, CH_3-C=N), 1.45 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.27 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 152.5, 146.7, 145.4, 144.3, 142.6, 142.3, 139.5 and 138.6 (C), 137.2 (CH), 136.0 (C), 130.5, 128.8, 128.2, 127.2, 126.6, 126.0, 125.9, 124.0, 121.3 and 117.2 (CH), 47.2 (CH_2), 44.3 (C), 37.0 (C), 31.3 (CH_3), 31.0 (CH_3), 30.1 (C), 29.7 (CH_3), 14.0 (CH_3); Found C, 70.3; H, 5.59; N, 11.02%. $C_{30}H_{28}O_4N_4$ requires C, 70.9; H, 5.51; N, 11.0%; m/z (FAB$^+$) 509.3 (100%, M^+).

General procedure for kinetic resolution of monotriflate 208 *via* Suzuki couplings



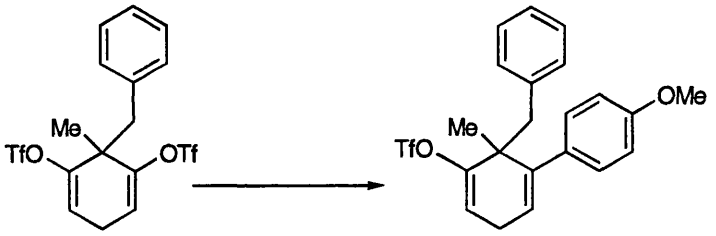
208 **222**

Dry THF (1 mL) was added to a mixture of triflate **208** (50.2 mg, 0.14 mmol), $Pd(OAc)_2$ (3.0 mg, 0.014 mmol, 10 mol%), a specific chiral ligand **L** (0.032 mmol, 22 mol% (monodentate) or 0.016 mmol, 11 mol% (bidentate)) and 4-methoxyphenylboronic acid (27.0 mg, 0.18 mmol). The resulting solution was stirred under nitrogen for 10 min then aqueous potassium hydroxide solution (1.78 M, 0.2 mL, 0.1 mmol) was added *via* syringe and the reaction was stirred at room temperature for the required time. The mixture was partitioned between water (5 mL) and EtOAc (5 mL). The aqueous layer was extracted with EtOAc (2 x 2 mL). The combined organic phases were then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (10% DCM/petrol) to give alkene **222**

and recovered starting material **208**. Enantiomeric purity was determined by chiral HPLC.

For ligands used in kinetic resolution of **208** see Tables 27 and 28.

General procedure for enantioselective desymmetrisation of ditriflate 209 *via* Suzuki couplings



209 **240**

Dry THF (1 mL) was added to a mixture of ditriflate **209** (0.10 mmol), 4-methoxyphenylboronic acid (19.0 mg, 0.125 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%) and the selected chiral ligand **L** (0.022 mmol (monodentate) or 0.011 mmol (bidentate)) and the resulting solution was stirred for 10 min under nitrogen. Aqueous potassium hydroxide solution (1.78 M, 0.2 mL, 0.11 mmol) was then added *via* syringe and the mixture was stirred at room temperature for the required time. The reaction mixture was partitioned between water (3 mL) and EtOAc (3 mL), the aqueous layer was extracted with EtOAc (2 x 3 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 10-30% DCM/petrol) to give recovered starting material **209** and monocoupled product **240.** Enantiomeric purity was measured by chiral HPLC.

For ligands used in enantioselective desymmetrisation of **209** see Table 30.

The best enantioselectivity (46% ee) was obtained from the desymmetrisation of ditriflate **209** with 4-methoxyphenylboronic acid **180** employing enantiopure ligand PHANEPHOS **105** (Table 30, Entry 4).

General procedure for enantioselective desymmetrisation of ditriflate 217 *via* Suzuki couplings

217 **247**

A-procedure with aqueous base (KOH aq)

Dry THF (1 mL) was added to a mixture of ditriflate **217** (46.6 mg, 0.10 mmol), 4-acetylphenylboronic acid (25.2 mg, 0.15 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%) and selected chiral ligand **L** (0.022 mmol (monodentate) or 0.011 mmol (bidentate)) and the resulting solution was stirred for 10 min under nitrogen. Aqueous potassium hydroxide solution (1.78 M, 0.06 mL, 0.10 mmol) was then added *via* syringe and the mixture was stirred at room temperature for the required time. The reaction mixture was partitioned between water (3 mL) and EtOAc (3 mL), the aqueous layer was extracted with EtOAc (2 x 3 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified

by flash chromatography (gradient elution 5-10% EtOAc/petrol) to give recovered starting material **217** and monotriflate **247.** Enantiomeric purity was determined by chiral HPLC.

For ligands used in enantioselective desymmetrisation of **217** see Tables 31,32.

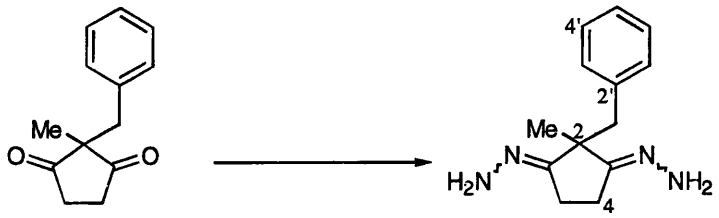
B-Procedure with solid base (Caesium fluoride)

Dry dioxane (1 mL) was added to a mixture of ditriflate **217** (46.6 mg, 0.10 mmol), 4-acetylphenylboronic acid (25.2 mg, 0.15 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 10 mol%), the selected chiral ligand **L** (0.022 mmol (monodentate) or 0.011 mmol (bidentate)) and caesium fluoride (45.6 mg, 0.3 mmol). The resulting solution was stirred for the required time and was then partitioned between water (3 mL) and EtOAc (3 mL), the aqueous layer was extracted with EtOAc (2 x 3 mL) and the combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution 5-10% EtOAc/petrol) to give recovered starting material **217** and monotriflate **247.** Enantiomeric purity was determined by chiral HPLC.

For ligands used in enantioselective desymmetrisation of **217** see Table 33.

The best enantioselectivity (71% ee, $[\alpha_D]^{23}$ = +70.0 (c 0.05, $CHCl_3$)) was obtained from the desymmetrisation of ditriflate **217** with 4-acetylphenylboronic acid **181** employing enantiopure ligand (*S*)-MeO-MOP **118** (Table 33, Entry 4).

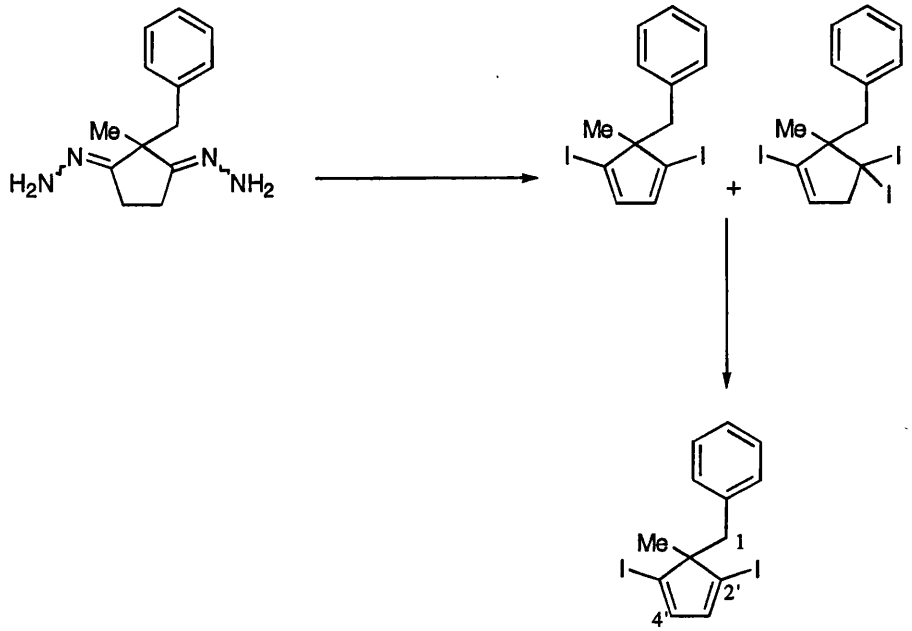
Preparation of 2-benzyl-2-methyl-1,3-cyclopentadione dihydrazone (272)



213 **272**

Triethylamine (7.40 mL, 53.1 mmol) was added to a stirred solution of the diketone **213** (1.5 g, 7.42 mmol) and monohydrate hydrazine (1.85 mL, 59.4 mmol) in absolute ethanol (10 mL). The reaction was then stirred and heated at 100 °C for 2 days. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in DCM (20 mL) and washed with water till neutrality. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure to give *dihydrazone* **272** (1.6 g, 94%) as a straw solid; mp 99-100 °C (from DCM/hexane); ν_{max} (film)/cm^{-1} 3378 (NH_2), 3210 (NH_2), 3028 (unsaturated CH), 2970 and 2926 (saturated CH), 1646 (C=N); δ_H (270 MHz, CD_3OD) 7.12-7.05 (3H, m, H-4', H-5', H-6'), 6.95-6.91 (2H, m, H-3', H-7'), 4.80 (4H, s, NH_2), 2.82 (2H, s, 2 x H-1'), 2.29 (2H, dd, *J* 18.3, 6.0, 1 x H-4, 1 x H-5), 1.61 (2H, dd, *J* 18.3, 6.0, 1 x H-4, 1 x H-5), 1.24 (3H, s, CH_3); δ_C (75 MHz, $CDCl_3$) 161.9 (C-1, C-3), 139.0 (Ar C), 130.4, 128.3 and 126.6 (5 x Ar CH), 51.5 (C-2), 50.2 (C-1'), 25.5 (CH_3), 23.8 (C-4, C-5); m/z (EI^+) 376.1 (100%, M^+); Found C, 67.8; H, 7.80; N, 24.3%. $C_{13}H_{18}N_4$ requires C, 67.82; H, 7.83; N, 24.35%.

Preparation of 1-((2,5-diodo-1-methyl-2,4-cyclopentadien-1-yl)methyl)benzene (273)



A solution of dihydrazone **272** (0.23 g, 1 mmol), and tetramethylguanidine (0.88 mL, 7 mmol) in dry DCM (10 mL) was added dropwise to a stirred solution of iodine (1.30 g, 5 mmol) in DCM (15 mL). The mixture was stirred for 20 min at room temperature after which time tlc (5% EtOAc/petrol) showed complete comsuption of the dihydrazone and formation of *gem*-iodide and the expected divinyliododide **273** (50/50 ratio). The mixture was concentrated under reduced pressure. The residue was dissolved in tetramethylguanidine (2 mL) and heated at 80 °C for 2 h. The reaction mixture was cooled to room temperature, diluted in DCM (20 mL), washed successively with 2N HCl (10 mL), 10 % sodium thiosulfate (10 mL), water till neutrality, aqueous sodium bisulfite (10 mL) and aqueous $NaHCO_3$. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (florisil, 5% EtOAc/petrol) to give *divinyliodide* **273** (268 mg, 68%) as a yellow oil; ν_{max} (neat)/cm^{-1} 3029 (unsaturated CH), 2962, 2923 and 2869

(saturated CH), 1603 (C=C); δ_H (300 MHz, $CDCl_3$) 7.26-7.19 (3H, m, Ar), 7.16-7.13 (2H, m, Ar), 6.44 (2H, s, H-3', H-4'), 2.82 (2H, s, 2 x H-1), 1.12 (3H, s, CH_3); δ_C (300 MHz, $CDCl_3$) 141.4 (C-3', C-4'), 136.1 (Ar C), 129.9, 127.8 and 127.0 (5 x Ar CH), 106.2 (C-2', C-5'), 63.2 (C-1'), 42.0 (C-1), 24.4 (CH_3); m/z (EI^+) 421.9 (100%, M^+); Found $M+NH_4^+$, 439.9369, $C_{13}H_{16}I_2N$ requires 439.9372.

References

1. Tsuji, J. in *Palladium and Catalysts-inovations in organic synthesis*; Wiley: Chichester, 1995.

2. Neubert, R.; Hinz, P.; Thiel, R.; Neubert, D. *Life Sci.* **1996**, *58*, 295.

3. For a recent review about organopalladium chemistry, see: Yamamoto, Y.; Negishi, E. *J. Organomet. Chem.* **1999**, *576*, 1-322.

4. Zovoki, T. M.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jp.* **1971**, *44*, 581.

5. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

6. Negishi, E.; Takahashi, T.; Baba, S.; Vanhorn, D. E.; Okukadon, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.

7. Kumada, M. *Pure App. Chem.* **1980**, *52*, 669.

8. Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 9374.

9. Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771.

10. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

11. Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* **1979**, 3437.

12. Suzuki, A. *Acc. Chem. Res.* **1982**, *15*, 178.

13. Suzuki, A. *Pure Appl. Chem.* **1985**, *57*, 1749.

14. Suzuki, A. *Pure Appl. Chem.* **1994**, *66*, 213.

15. DeMeijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1995**, *33*, 2379.

16. Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2.

17. Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738.

18. Sato, Y.; Honda, T.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593.

19. Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953.

20. Kojima, A.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *88*, 5459.

21. Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965.

22. Shibasaki, M.; Mase, T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090.

23. Fukuzawa, A.; Sato, H.; Masamune, T. *Tetrahedron Lett.* **1987**, *28*, 4303.

24. Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398.

25. Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371.

26. Kagechika, K.; Oshima, T.; Shibasaki, M. *Tetrahedron* **1993**, *49*, 1773.

27. Nylund, C. S.; Klopp, J. M.; Weinreb, S. M. *Tetrahedron Lett.* **1994**, *35*, 4287.

28. Fuji, F. *Chem. Rev.* **1993**, *93*, 2037.

29. Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 388.

30. Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846.

31. Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571.

32. Gorman, D. G.; Cummings, J. L. *Neurospy. Neurospy. BE* **1993**, *6*, 229.

33. Davies, P. *Clin. Neuropharmacol.* **1991**, *14*, S24.

34. Yu, Q.-S.; Brossi, A. *Heterocycles* **1988**, *27*, 745.

35. Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.

36. Pfaltz, A. *Acta Chem. Scand.* **1996**, *50*, 189.

37. Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505.

38. Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis-Stuttgart* **1997**, *11*, 1338.

39. Miyazaki, F.; Uotsu, K.; Shibasaki, M. *Tetrahedron* **1998**, *54*, 13073.

40. Andersen, N. G.; Parvez, M.; Keay, B. A. *Org. Lett.* **2000**, *2*, 2817.

41. Hayashi, M.; Keenan, M.; Pfaltz, A., unplublished results.

42. Consiglio, G.; Botteghi, C. *Helv. Chim. Acta* **1973**, *56*, 460.

43. Kiso, Y.; Tamao, K.; Miyake, N.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett.* **1974**, 3.

44. Hayashi, T.; Shima, M. F.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1980**, *21*, 79.

45. Tamao, K.; Yamamoto, H.; Matsumoto, H.; Miyake, N.; Hayashi, T.; Kumada, M. *Tetrahedron Lett.* **1977**, 1389.

46. Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.

47. Hayashi, T.; Konishi, M.; Fukushimo, M.; Mise, T.; Kagotani, M.; Tajika, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 180.

48. Hayashi, T.; Konishi, M.; Shima, M. F.; Kaneshira, K.; Hioki, T.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195.

49. Chan, T. H.; Fleming, I. *Synthesis-Stuttgart* **1979**, 761.

50. Colvin, E. W. In *Silicon in organic synthesis*; Butterworths; London, 1981; pp 97.

51. Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962.

52. Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772.

53. Hayashi, T.; Hagihara, T.; Katsuro, Y.; Kumada, M. *Bull. Chem. Soc. Jp.* **1983**, *56*, 363.

54. Hayashi, T.; Yamamoto, A.; Hojo, M.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 495.

55. Kreuzfeld, H.-J.; Döbler, C.; Abicht, H. P. *J. Organomet. Chem.* **1987**, *336*, 287.

56. Uemura, M.; Miyake, R.; Nishimura, H.; Matsumoto, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1992**, *3*, 213.

57. Yamada, M.; Yamashita, M. *Carbohydrate Res.* **1981**, *95*, C9.

58. Yamashita, M.; Hiramatsu, K.; Suzuki, N.; Inokawa, S. *Bull. Chem. Soc. Jp.* **1982**, *55*, 2917.

59. Yamashita, M.; Kobayashi, M.; Tsunekawa, K.; Sugiura, M.; Oshikawa, T. *Carbohydrate Res.* **1984**, *C6*, 131.

60. Iida, A.; Yamashita, M. *Bull. Chem. Soc. Jp.* **1988**, *61*, 2365.

61. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

62. Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

63. Cammidge, A.; Crépy, K. V. L. *J. Chem. Soc., Chem. Commun.* **2000**, 1723.

64. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051.

65. Williams, J. M. J. *Synlett* **1996**, 705.

66. Trost, B. M.; Van Vranken, D. L. V. *Chem. Rev.* **1996**, *96*, 395.

67. Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738.

68. Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

69. Ward, R. S. *J. Chem. Soc., Chem. Rev.* **1990**, *19*, 1.

70. Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9.

71. Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167.

72. Trost, B. M.; Kallander, L. S. *J. Org. Chem.* **1999**, *64*, 5427.

73. Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 3695.

74. Dokuzokic, Z.; Roberts, N. K.; Sawyer, J. F.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1986**, *108*, 2034.

75. Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525.

76. Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765.

77. Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532 and 7171.

78. Sharpless, K. B.; Katsuki, T. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

79. Sharpless, K. B.; Finn, M. G. In *Asymmetric synthesis*; Morisson J. D., Ed.; New York, 1985; Vol. 5.

80. Smith, D. B.; Wang, Z. Y.; Schreiber, S. L. *Tetrahedron* **1990**, *46*, 4793.

81. Whitesell, J. K.; Allen, D. F. *J. Org. Chem.* **1985**, *50*, 3025.

82. Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754.

83. Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655.

84. Arai, S.; Hamaguchi, S.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 2997.

85. Brasë, S. *Synlett* **1999**, *10*, 1654.

86. Webel, M.; Reissig, H. U. *Synlett* **1997**, 1141.

87. Narula, C. K.; Mak, K. T.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2792.

88. Overman, L. E.; Renaldo, A. F. *J. Am. Chem. Soc.* **1990**, *112*, 3945.

89. Brunner, H.; Kramler, K. *Synthesis* **1991**, 1121.

90. Ozawa, F.; Kobatake, Y.; Kubo, A.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1994**, 1323.

91. Namyslo, J. C.; Kaufmann, D. E. *Synlett* **1994**, 804.

92. Miyano, S.; Tobita, M.; Hashimoto, M. *Bull. Chem. Soc. Jp.* **1981**, *4*, 3522.

93. Yamamoto, K.; Fukushima, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1490.

94. Takashi, K.; Hayashi, T. *Tetrahedron* **1999**, *55*, 3455.

95. Hayashi, T. *Acc. Chem. Res.* **1999**, *33*, 354.

96. Takashi, K.; Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* **1996**, *37*, 3161.

97. Uemura, M.; Nishimura, H.; Hayashi, T. *J. Organomet. Chem.* **1994**, *473*, 129.

98. Scot, W. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1755.

99. Carpentier, J. F.; Castanet, Y.; Brocard, J.; Mortreux, A.; Petit, F. *Tetrahedron Lett.* **1992**, *33*, 2001.

100. Cho, S. Y.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3751.

101. Uozumi, Y.; Tanahashi, A.; Lee, S. Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945.

102. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.

103. Gotov, B.; Schmalz, H.-G. *Org. Lett.* **2001**, *3*, 1753.

104. Hayashi, T.; Hayashi, C.; Uozumi, Y. *Tetrahedron: Asymmetry* **1995**, *6*, 2503.

105. Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419.

106. Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Kumada, M.; Yamamoto, K. *Bull. Chem. Soc. Jp.* **1980**, *53*, 1138.

107. Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509.

108. Brown, H. C.; Hammar, W. J. *Tetrahedron* **1978**, *34*, 3405.

109. Amatore, C.; Azzahi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 1670.

110. Morton, D. R.; Brokaw, F. C. *J. Org. Chem.* **1979**, *44*, 2880.

111. Konishi, Y.; Kawamura, M.; Igushi, Y.; Arai, Y.; Hayashi, M. *Tetrahedron* **1981**, *37*, 4391.

112. Mori, K.; Tsuji, M. *Tetrahedron* **1986**, *42*, 435.

113. Eymery, F.; Iorga, B.; Savignac, P. *Synthesis-Stuttgart* **2000**, 576.

114. Neidlein, R.; Winter, M. *Synthesis-Stuttgart* **1998**, 1362.

115. Ramirez, F.; Desai, N. B.; Kelvie, N. M. *J. Am. Chem. Soc.* **1962**, *84*, 1745.

116. Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

117. Savignac, P.; Coutrot, P. *Synthesis-Stuttgart* **1976**, 197.

118. Fisher, R. P.; On, H. P.; Snow, J. T.; Zweifel, G. *Synthesis-Stuttgart* **1982**, 127.

119. Nuss, J. M.; Rennels, R. A.; Levine, B. H. *J. Am. Chem. Soc.* **1993**, *115*, 6991.

120. Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1996**, *61*, 5716.

121. Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551.

122. Scott, A. F.; Chen, H.; Kunz, R. K.; Schnaderbeck, M. J.; Roush, W. R. *Org. Lett.* **2000**, *2*, 2691.

123. Minato, A.; Suzuki, K.; Tamao, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257.

124. Minato, A. *J. Org. Chem.* **1991**, *56*, 4052.

125. Rossi, R.; Carpita, A. *Tetrahedron Lett.* **1986**, *27*, 2529.

126. George, J. H. B.; Rolfe, J. A.; Woodward, L. A. *Trans. Faraday Soc.* **1953**, *49*, 375.

127. Roush, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710.

128. Uenishi, J.; Beau, J.-M.; Amstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc.* **1987**, *109*, 4756.

129. Soderquist, J. A.; Leõn, G.; Coberg, J. C.; Martinez, I. *Tetrahedron Lett.* **1995**, *36*, 3119.

130. Miller, M. W.; Bauer, A.; Vice, S. F.; McCombie, S. W. *Synlett* **2001**, *2*, 254.

131. Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873.

132. Wang, L.; Shen, W. *Tetrahedron Lett.* **1998**, *39*, 7625.

133. Hanisch, I.; Brückner, R. *Synlett* **2000**, *3*, 374.

134. Retz, S. H.; Cook, M.; Gawish, A.; Reiss, U. *Org. Synt.* **1986**, *64*, 27.

135. Piers, E.; Karunaratne, V. *Can. J. Chem.* **1989**, *67*, 160.

136. Posner, G. H.; Loomis, G. L.; Sawaya, H. S. *Tetrahedron Lett.* **1975**, *16*, 1373.

137. Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

138. Wright, S. W.; Hageman, D. L.; Clure, L. D. M. *J. Org. Chem.* **1994**, *59*, 6095.

139. Anderson, J. C.; Namli, H.; Roberts, C. A. *Tetrahedron* **1997**, *53*, 15123.

140. Stang, P. J.; Summerville, R. *J. Am. Chem. Soc.* **1969**, *91*, 4600.

141. Stang, P. J.; Rappoport, Z.; Hanack, M.; Subramanian, L. R. in *Vinylcations*: New York, 1979.

142. Stang, P. J. *Acc. Chem. Res.* **1978**, *11*, 107.

143. Huang, W.-Y.; Chen, O.-Y. In *the chemistry of sulfonic acids, esters and their derivatives*; Patai, S.; Rapapport, Z., Ed.; Chichester: Wiley, 1991; pp 903.

144. Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis-Stuttgart* **1982**, 85.

145. Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386.

146. Godart, A.; Rovera, J.-C.; Marsais, F.; Plé, N.; Quéguiner, G. *Tetrahedron* **1992**, *48*, 4123.

147. Conway, S. C.; Gribble, G. W. *Heterocycles* **1990**, *30*, 627.

148. Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

149. Robl, J. A. *Synthesis-Stuttgart* **1991**, 56.

150. Stang, P. J.; Treptow, W. *Synthesis-Stuttgart* **1980**, 283.

151. Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, *26*, 3787.

152. Rano, T. A.; Greenlee, M. L.; Dininno, F. P. *Tetrahedron Lett.* **1990**, *31*, 2853.

153. Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

154. Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.* **1990**, *55*, 1589.

155. Heathcock, C. M. In *Modern synthetic method*; Sheffold R., Ed.; Springer Verlag: Berlin; 1992; vol 6, pp 6299.

156. McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979.

157. Comins, D. L.; Dehghani, A. D. *Tetrahedron Lett.* **1992**, *33*, 6299.

158. Subramanian, L. R.; Bentz, H.; Hanack, M. *Synthesis-Stuttgart* **1973**, 293.

159. Hirsch, E.; Hünig, S.; Reibig, H.-U. *Chem. Ber.* **1982**, *115*, 3687.

160. Hanack, M.; Auchter, C. *J. Am. Chem. Soc.* **1985**, *107*, 5238.

161. Farina, V.; Baker, S. R.; Hauck, S. I. *J. Org. Chem.* **1989**, *54*, 4962.

162. Philips, D.; O'Neill, B. T. *Tetrahedron Lett.* **1990**, *31*, 3291.

163. Lee, J. N.; Li, J.-H.; Oya, S.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5301.

164. Renouf, P.; Poirier, J. M.; Duhamel, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1739.

165. Stetter, H. In *Newer methods of preparative organic chemistry*; Foerst, W., Ed.; Academic: New york; 1963; Vol. 2.

166. Mahajan, J. R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1434.

167. Fanta, P. E. *Synthesis-Stuttgart* **1974**, 9.

168. Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *39*, 2559.

169. Dyker, G.; Körning, J.; Jones, P. G.; Bubenitschek, P. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1733.

170. Cliff, M. D.; Pyne, S. G. *Synthesis-Stuttgart* **1994**, 681.

171. Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793.

172. Hennings, D. D.; Rawal, V. H.; Iwama, T. *Org. Lett.* **1999**, *1*, 1205.

173. Qabaja, G.; Jones, G. B. *Tetrahedron Lett.* **2000**, *41*, 5317.

174. Wang, L.; Shevlin, P. B. *Tetrahedron Lett.* **2000**, *41*, 285.

175. Ames, D. E.; Opalko, A. *Synthesis-Stuttgart* **1983**, 234.

176. Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.

177. Smet, M.; Dijk, J. V.; Dehaen, W. *Synlett* **1999**, *4*, 495.

178. Rice, J. E.; Cai, Z.-W. *Tetrahedron Lett.* **1992**, *33*, 1675.

179. Bringmann, G.; Jansen, J. R.; Rink, H.-P. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 913.

180. Deshpande, P. P.; Martin, O. R. *Tetrahedron Lett.* **1990**, *31*, 6313.

181. Bringmann, G.; Jansen, J. R.; Reusher, H.; Rübenacker, M. *Tetrahedron Lett.* **1990**, *31*, 643.

182. M-Mañas, M.; Pérez, M.; Pleixtas, R. *J. Org. Chem.* **1996**, *61*, 2346.

183. Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978.

184. Schoenberg, A.; Heck, R. F. *J. Am. Chem. Soc.* **1974**, *96*, 7761.

185. Stille, J. K.; Wong, P. K. *J. Org. Chem.* **1975**, *40*, 532.

186. Hidai, M.; Hikita, T.; Wada, Y.; Fujikura, Y.; Uchida, Y. *Bull. Chem. Soc. Jp.* **1974**, *48*, 3318.

187. Holt, D. A.; Levy, M. A.; Ladd, D. L.; Oh, H.-J.; Erb, J. M.; Heaslip, J. I.; Brandt, M.; Metcalf, B. W. *J. Med. Chem.* **1990**, *33*, 937.

188. Farina, V.; Baker, S. R.; Sapino, C. *Tetrahedron Lett.* **1988**, *29*, 6043.

189. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.

190. Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1986**, *27*, 5541.

191. Farina, V.; Baker, S. R.; Benigni, D. A.; Hauck, S. I.; Sapino, C. *J. Org. Chem.* **1990**, *55*, 5833.

192. Behforouz, M.; Bolan, J. L.; Flynt, M. S. *J. Org. Chem.* **1985**, *50*, 1186.

193. Pasteur, L. C. *R. Hebd. Seance Acad. Sci. Paris* **1857**, *45*, 1032.

194. Kagan, H. B.; Fiaud, J. C. In *Topics in stereochemistry*; E. L. Eliel, S. H. Wilen, Ed.; Wiley: New York, Chichester, 1988; Vol. 18.

195. Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synt. Cat.* **2001**, *343*, 5.

196. Kutsuki, H.; Sawa, I.; Hasegawa, J.; Watanabe, K. *Agric. Biol. Chem.* **1986**, *50*, 2369.

197. Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 397.

198. Schurig, V.; Giv-Av, E. *Isr. J. Chem.* **1977**, *15*, 96.

199. Breeden, S.; Wills, M. *J. Org. Chem.* **1999**, *64*, 9735.

200. Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104.

201. Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3889.

202. Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

203. Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485.

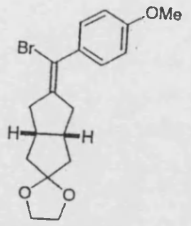
204. Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352.

205. Jaeger, W.; House, H. O. *Org. Synt.* **1970**, *54*, 79.

206. Anderson, A. G.; Stang, P. J. *J. Org. Chem.* **1976**, *41*, 3034.

Appendix-1

^{1}H NMR of monobromide 182



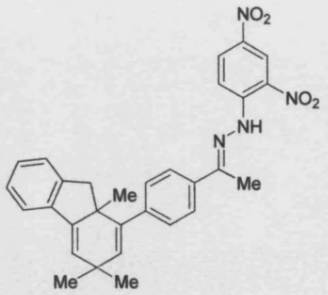
C190.4

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr2"

PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.561 sec
Width 4797.5 Hz
32 repetitions
OBSERVE H1, 399.7890770 MHz
DATA PROCESSING
FT size 32768
Total time 1 min, 58 sec

Appendix-2

X-Ray crystal structure of hydrazone 256



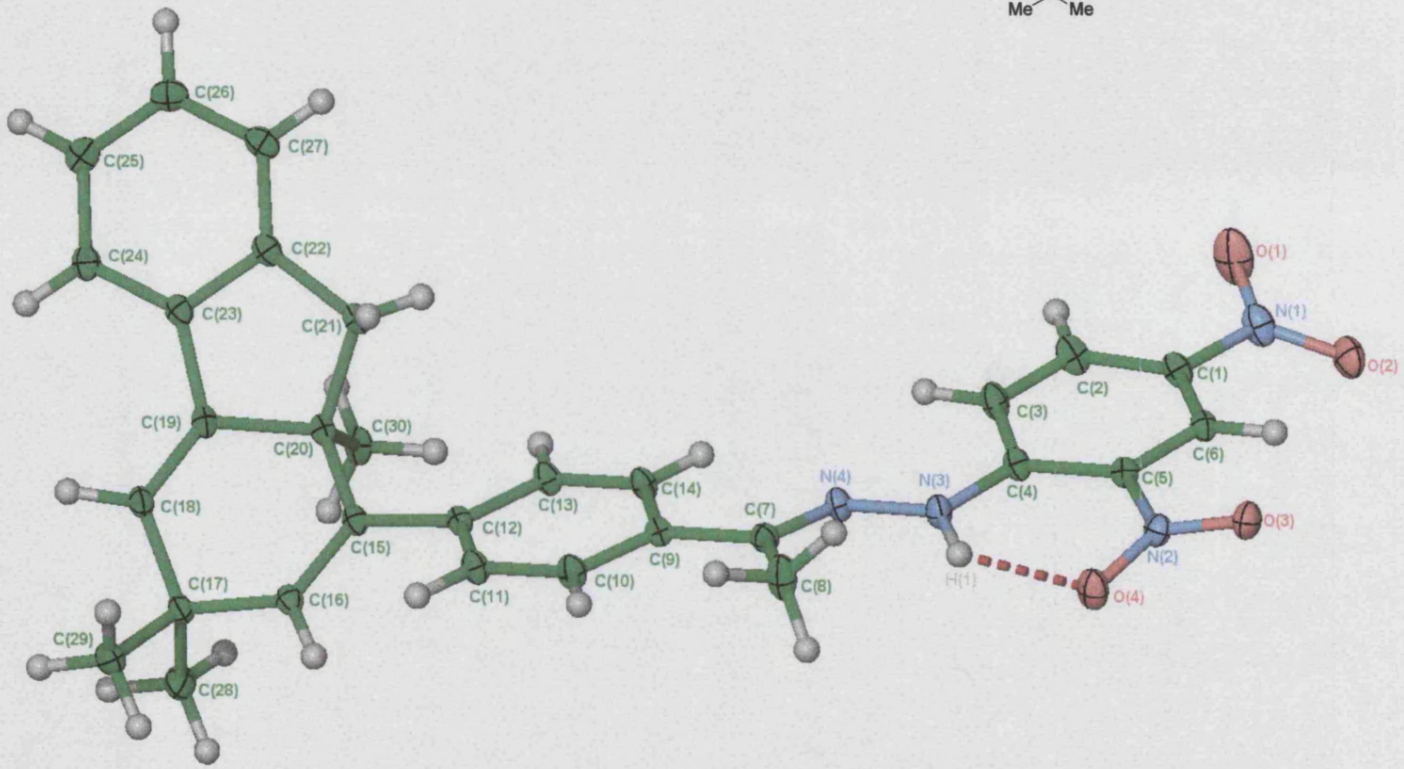


Table 1. Crystal data and structure refinement for 1.

Identification code	k01mcw1a
Empirical formula	C30 H28 N4 O4
Formula weight	508.5
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 9.20400(10)Å α = 90°
	b = 16.1930(2)Å β = 90°
	c = 34.3440(5)Å γ = 90°
Volume	5118.64(11) $Å^3$
Z	8
Density (calculated)	1.320 Mg/m^3
Absorption coefficient	0.089 mm^{-1}
F(000)	2144
Crystal size	0.30 x 0.30 x 0.13 mm
Theta range for data collection	3.56 to 28.26°
Index ranges	-12<=h<=12; -21<=k<=21; -45<=l<=45
Reflections collected	40645
Independent reflections	6112 [R(int) = 0.0911]
Reflections observed (>2σ)	3998
Data Completeness	0.963
Max. and min. transmission	0.9889 and 0.9737
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6112 / 0 / 351
Goodness-of-fit on F^2	0.957
Final R indices [I>2σ(I)]	R_1 = 0.0594 wR_2 = 0.1352
R indices (all data)	R_1 = 0.1016 wR_2 = 0.1606
Largest diff. peak and hole	0.343 and -0.323 $eÅ^{-3}$

Notes: H1 located and freely refined.

Hydrogen bonds with H..A < r(A) + 2.000 Angstroms and <DHA > 110 deg.

D-H	d(D-H)	d(H..A)	<DHA	d(D..A)	A
N3-H1	0.903	1.916	132.98	2.617	O4

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(1)	2777(2)	-558(2)	-681(1)	71(1)
O(2)	3606(2)	-1306(1)	-1159(1)	49(1)
O(3)	8108(2)	-421(1)	-1726(1)	39(1)
O(4)	9864(2)	-47(1)	-1348(1)	44(1)
N(1)	3763(2)	-780(1)	-902(1)	44(1)
N(2)	8558(2)	-200(1)	-1409(1)	31(1)
N(3)	9274(2)	602(1)	-669(1)	33(1)
N(4)	9573(2)	935(1)	-308(1)	32(1)
C(1)	5173(2)	-396(1)	-855(1)	34(1)
C(2)	5475(2)	37(2)	-511(1)	40(1)
C(3)	6822(2)	360(2)	-451(1)	38(1)
C(4)	7932(2)	285(1)	-735(1)	31(1)
C(5)	7547(2)	-115(1)	-1089(1)	28(1)
C(6)	6180(2)	-455(1)	-1146(1)	30(1)
C(7)	10781(2)	1327(1)	-270(1)	29(1)
C(8)	11817(3)	1482(2)	-602(1)	50(1)
C(9)	11088(2)	1656(1)	124(1)	27(1)
C(10)	12398(2)	2035(1)	224(1)	34(1)
C(11)	12649(2)	2317(1)	597(1)	33(1)
C(12)	11614(2)	2240(1)	893(1)	28(1)
C(13)	10290(2)	1875(1)	789(1)	31(1)
C(14)	10041(2)	1589(1)	417(1)	31(1)
C(15)	11940(2)	2522(1)	1298(1)	28(1)
C(16)	13291(2)	2465(1)	1439(1)	30(1)
C(17)	13790(2)	2739(1)	1837(1)	32(1)
C(18)	12737(2)	3364(1)	1998(1)	32(1)
C(19)	11383(2)	3428(1)	1867(1)	29(1)
C(20)	10737(2)	2858(1)	1556(1)	28(1)
C(21)	9594(2)	3424(1)	1352(1)	31(1)
C(22)	9234(2)	4062(1)	1658(1)	31(1)
C(23)	10279(2)	4059(1)	1955(1)	30(1)
C(24)	10172(2)	4607(1)	2266(1)	33(1)
C(25)	9013(2)	5156(1)	2276(1)	37(1)
C(26)	7990(2)	5166(2)	1982(1)	38(1)
C(27)	8095(2)	4617(1)	1671(1)	35(1)
C(28)	13927(3)	1986(2)	2111(1)	46(1)
C(29)	15311(2)	3131(2)	1799(1)	45(1)
C(30)	9913(2)	2163(1)	1774(1)	34(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

O(1)-N(1)	1.237(3)	O(2)-N(1)	1.234(3)
O(3)-N(2)	1.221(2)	O(4)-N(2)	1.245(2)
N(1)-C(1)	1.448(3)	N(2)-C(5)	1.446(3)
N(3)-C(4)	1.356(3)	N(3)-N(4)	1.380(2)
N(3)-H(1)	0.90(3)	N(4)-C(7)	1.287(3)
C(1)-C(6)	1.367(3)	C(1)-C(2)	1.401(3)
C(2)-C(3)	1.362(3)	C(2)-H(2)	0.9500
C(3)-C(4)	1.416(3)	C(3)-H(3)	0.9500
C(4)-C(5)	1.423(3)	C(5)-C(6)	1.387(3)
C(6)-H(6)	0.9500	C(7)-C(9)	1.482(3)
C(7)-C(8)	1.506(3)	C(8)-H(8A)	0.9800
C(8)-H(8B)	0.9800	C(8)-H(8C)	0.9800
C(9)-C(14)	1.399(3)	C(9)-C(10)	1.396(3)
C(10)-C(11)	1.381(3)	C(10)-H(10)	0.9500
C(11)-C(12)	1.398(3)	C(11)-H(11)	0.9500
C(12)-C(13)	1.401(3)	C(12)-C(15)	1.494(3)
C(13)-C(14)	1.376(3)	C(13)-H(13)	0.9500
C(14)-H(14)	0.9500	C(15)-C(16)	1.338(3)
C(15)-C(20)	1.518(3)	C(16)-C(17)	1.507(3)
C(16)-H(16)	0.9500	C(17)-C(18)	1.506(3)
C(17)-C(29)	1.542(3)	C(17)-C(28)	1.545(3)
C(18)-C(19)	1.330(3)	C(18)-H(18)	0.9500
C(19)-C(23)	1.473(3)	C(19)-C(20)	1.532(3)
C(20)-C(30)	1.551(3)	C(20)-C(21)	1.560(3)
C(21)-C(22)	1.510(3)	C(21)-H(21A)	0.9900
C(21)-H(21B)	0.9900	C(22)-C(27)	1.382(3)
C(22)-C(23)	1.401(3)	C(23)-C(24)	1.391(3)
C(24)-C(25)	1.389(3)	C(24)-H(24)	0.9500
C(25)-C(26)	1.382(3)	C(25)-H(25)	0.9500
C(26)-C(27)	1.393(3)	C(26)-H(26)	0.9500
C(27)-H(27)	0.9500	C(28)-H(28A)	0.9800
C(28)-H(28B)	0.9800	C(28)-H(28C)	0.9800
C(29)-H(29A)	0.9800	C(29)-H(29B)	0.9800
C(29)-H(29C)	0.9800	C(30)-H(30A)	0.9800
C(30)-H(30B)	0.9800	C(30)-H(30C)	0.9800
O(2)-N(1)-O(1)	123.7(2)	O(2)-N(1)-C(1)	118.7(2)
O(1)-N(1)-C(1)	117.6(2)	O(3)-N(2)-O(4)	122.35(18)
O(3)-N(2)-C(5)	119.21(17)	O(4)-N(2)-C(5)	118.44(17)
C(4)-N(3)-N(4)	118.71(18)	C(4)-N(3)-H(1)	115.9(18)
N(4)-N(3)-H(1)	124.7(18)	C(7)-N(4)-N(3)	117.04(17)
C(6)-C(1)-C(2)	121.13(19)	C(6)-C(1)-N(1)	119.7(2)
C(2)-C(1)-N(1)	119.1(2)	C(3)-C(2)-C(1)	120.1(2)
C(3)-C(2)-H(2)	120.0	C(1)-C(2)-H(2)	120.0
C(2)-C(3)-C(4)	121.3(2)	C(2)-C(3)-H(3)	119.3
C(4)-C(3)-H(3)	119.3	N(3)-C(4)-C(3)	120.61(19)
N(3)-C(4)-C(5)	122.87(19)	C(3)-C(4)-C(5)	116.50(18)
C(6)-C(5)-C(4)	121.92(19)	C(6)-C(5)-N(2)	115.96(18)
C(4)-C(5)-N(2)	122.11(18)	C(1)-C(6)-C(5)	118.87(19)

C(1)-C(6)-H(6)	120.6	C(5)-C(6)-H(6)	120.6
N(4)-C(7)-C(9)	115.64(18)	N(4)-C(7)-C(8)	123.65(19)
C(9)-C(7)-C(8)	120.67(18)	C(7)-C(8)-H(8A)	109.5
C(7)-C(8)-H(8B)	109.5	H(8A)-C(8)-H(8B)	109.5
C(7)-C(8)-H(8C)	109.5	H(8A)-C(8)-H(8C)	109.5
H(8B)-C(8)-H(8C)	109.5	C(14)-C(9)-C(10)	116.90(19)
C(14)-C(9)-C(7)	119.95(18)	C(10)-C(9)-C(7)	123.14(18)
C(11)-C(10)-C(9)	121.17(19)	C(11)-C(10)-H(10)	119.4
C(9)-C(10)-H(10)	119.4	C(10)-C(11)-C(12)	122.13(19)
C(10)-C(11)-H(11)	118.9	C(12)-C(11)-H(11)	118.9
C(11)-C(12)-C(13)	116.37(18)	C(11)-C(12)-C(15)	120.84(18)
C(13)-C(12)-C(15)	122.78(18)	C(14)-C(13)-C(12)	121.62(19)
C(14)-C(13)-H(13)	119.2	C(12)-C(13)-H(13)	119.2
C(13)-C(14)-C(9)	121.80(19)	C(13)-C(14)-H(14)	119.1
C(9)-C(14)-H(14)	119.1	C(16)-C(15)-C(12)	120.17(19)
C(16)-C(15)-C(20)	119.44(18)	C(12)-C(15)-C(20)	120.38(17)
C(15)-C(16)-C(17)	126.2(2)	C(15)-C(16)-H(16)	116.9
C(17)-C(16)-H(16)	116.9	C(16)-C(17)-C(18)	109.57(16)
C(16)-C(17)-C(29)	108.79(19)	C(18)-C(17)-C(29)	109.74(17)
C(16)-C(17)-C(28)	110.14(17)	C(18)-C(17)-C(28)	110.99(19)
C(29)-C(17)-C(28)	107.57(19)	C(19)-C(18)-C(17)	122.07(19)
C(19)-C(18)-H(18)	119.0	C(17)-C(18)-H(18)	119.0
C(18)-C(19)-C(23)	129.19(19)	C(18)-C(19)-C(20)	123.6(2)
C(23)-C(19)-C(20)	107.07(17)	C(15)-C(20)-C(19)	109.84(16)
C(15)-C(20)-C(30)	112.21(17)	C(19)-C(20)-C(30)	106.87(16)
C(15)-C(20)-C(21)	116.18(16)	C(19)-C(20)-C(21)	102.68(16)
C(30)-C(20)-C(21)	108.27(17)	C(22)-C(21)-C(20)	103.82(16)
C(22)-C(21)-H(21A)	111.0	C(20)-C(21)-H(21A)	111.0
C(22)-C(21)-H(21B)	111.0	C(20)-C(21)-H(21B)	111.0
H(21A)-C(21)-H(21B)	109.0	C(27)-C(22)-C(23)	120.0(2)
C(27)-C(22)-C(21)	129.32(19)	C(23)-C(22)-C(21)	110.65(18)
C(24)-C(23)-C(22)	120.5(2)	C(24)-C(23)-C(19)	130.45(19)
C(22)-C(23)-C(19)	109.05(18)	C(25)-C(24)-C(23)	118.8(2)
C(25)-C(24)-H(24)	120.6	C(23)-C(24)-H(24)	120.6
C(26)-C(25)-C(24)	120.8(2)	C(26)-C(25)-H(25)	119.6
C(24)-C(25)-H(25)	119.6	C(25)-C(26)-C(27)	120.4(2)
C(25)-C(26)-H(26)	119.8	C(27)-C(26)-H(26)	119.8
C(22)-C(27)-C(26)	119.4(2)	C(22)-C(27)-H(27)	120.3
C(26)-C(27)-H(27)	120.3	C(17)-C(28)-H(28A)	109.5
C(17)-C(28)-H(28B)	109.5	H(28A)-C(28)-H(28B)	109.5
C(17)-C(28)-H(28C)	109.5	H(28A)-C(28)-H(28C)	109.5
H(28B)-C(28)-H(28C)	109.5	C(17)-C(29)-H(29A)	109.5
C(17)-C(29)-H(29B)	109.5	H(29A)-C(29)-H(29B)	109.5
C(17)-C(29)-H(29C)	109.5	H(29A)-C(29)-H(29C)	109.5
H(29B)-C(29)-H(29C)	109.5	C(20)-C(30)-H(30A)	109.5
C(20)-C(30)-H(30B)	109.5	H(30A)-C(30)-	109.5

		H(30B)	
C(20)-C(30)-H(30C)	109.5	H(30A)-C(30)-H(30C)	109.5
H(30B)-C(30)-H(30C)	109.5		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement
factor exponent takes the form: $-2 \pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U$

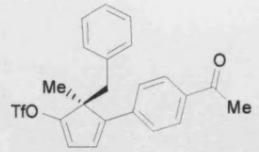
Atom	U11	U22	U33	U23	U13	U12
O(1)	44(1)	112(2)	58(1)	-15(1)	17(1)	-34(1)
O(2)	42(1)	48(1)	57(1)	-2(1)	-8(1)	-17(1)
O(3)	45(1)	42(1)	31(1)	-7(1)	1(1)	-6(1)
O(4)	31(1)	58(1)	44(1)	-12(1)	5(1)	-15(1)
N(1)	38(1)	57(1)	38(1)	6(1)	0(1)	-18(1)
N(2)	34(1)	28(1)	32(1)	-2(1)	2(1)	-6(1)
N(3)	30(1)	39(1)	29(1)	-4(1)	-1(1)	-7(1)
N(4)	32(1)	40(1)	24(1)	-1(1)	-4(1)	-6(1)
C(1)	30(1)	42(1)	31(1)	7(1)	-3(1)	-10(1)
C(2)	34(1)	61(2)	25(1)	4(1)	3(1)	-9(1)
C(3)	36(1)	55(1)	23(1)	-2(1)	-2(1)	-8(1)
C(4)	31(1)	35(1)	26(1)	3(1)	-4(1)	-6(1)
C(5)	30(1)	28(1)	26(1)	2(1)	0(1)	-4(1)
C(6)	32(1)	28(1)	29(1)	1(1)	-5(1)	-5(1)
C(7)	25(1)	33(1)	29(1)	-2(1)	0(1)	-2(1)
C(8)	37(1)	74(2)	38(2)	-17(1)	8(1)	-18(1)
C(9)	27(1)	30(1)	25(1)	2(1)	0(1)	-3(1)
C(10)	28(1)	43(1)	31(1)	0(1)	3(1)	-9(1)
C(11)	27(1)	39(1)	33(1)	1(1)	-2(1)	-9(1)
C(12)	29(1)	27(1)	28(1)	3(1)	-6(1)	-4(1)
C(13)	26(1)	42(1)	26(1)	1(1)	0(1)	-8(1)
C(14)	23(1)	40(1)	30(1)	1(1)	-2(1)	-8(1)
C(15)	30(1)	26(1)	27(1)	4(1)	-4(1)	-7(1)
C(16)	31(1)	27(1)	31(1)	2(1)	-4(1)	-3(1)
C(17)	32(1)	29(1)	35(1)	-1(1)	-13(1)	-1(1)
C(18)	34(1)	28(1)	34(1)	-2(1)	-10(1)	-4(1)
C(19)	33(1)	29(1)	26(1)	2(1)	-5(1)	-7(1)
C(20)	27(1)	30(1)	26(1)	2(1)	-4(1)	-6(1)
C(21)	27(1)	36(1)	29(1)	2(1)	-5(1)	-3(1)
C(22)	25(1)	37(1)	32(1)	4(1)	1(1)	-6(1)
C(23)	27(1)	29(1)	33(1)	4(1)	-1(1)	-7(1)
C(24)	35(1)	33(1)	32(1)	1(1)	0(1)	-8(1)
C(25)	39(1)	35(1)	38(1)	0(1)	10(1)	-6(1)
C(26)	31(1)	41(1)	43(1)	6(1)	10(1)	2(1)
C(27)	24(1)	44(1)	37(1)	8(1)	3(1)	-2(1)
C(28)	64(2)	36(1)	40(1)	-1(1)	-21(1)	7(1)
C(29)	32(1)	42(1)	61(2)	-11(1)	-14(1)	-1(1)
C(30)	39(1)	35(1)	27(1)	1(1)	1(1)	-13(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

Atom	x	y	z	U(eq)
H(2)	4739	104	-320	48
H(3)	7021	642	-215	45
H(6)	5948	-725	-1384	36
H(8A)	12409	987	-646	74
H(8B)	12452	1948	-537	74
H(8C)	11265	1610	-838	74
H(10)	13131	2100	31	41
H(11)	13554	2571	655	40
H(13)	9547	1822	979	37
H(14)	9132	1340	359	37
H(16)	14004	2229	1273	35
H(18)	13051	3723	2200	38
H(21A)	10009	3687	1117	37
H(21B)	8720	3105	1278	37
H(24)	10880	4606	2467	40
H(25)	8922	5528	2488	44
H(26)	7209	5549	1992	46
H(27)	7390	4625	1469	42
H(28A)	14281	2169	2366	70
H(28B)	14612	1588	1999	70
H(28C)	12974	1724	2141	70
H(29A)	15253	3621	1632	67
H(29B)	15982	2730	1684	67
H(29C)	15663	3291	2058	67
H(30A)	9473	1786	1585	51
H(30B)	9151	2406	1937	51
H(30C)	10596	1856	1939	51
H(1)	9940(30)	504(17)	-855(8)	54(8)

Appendix-3

X-ray crystal structure of monotriflate (*S*)-247 (97% ee)



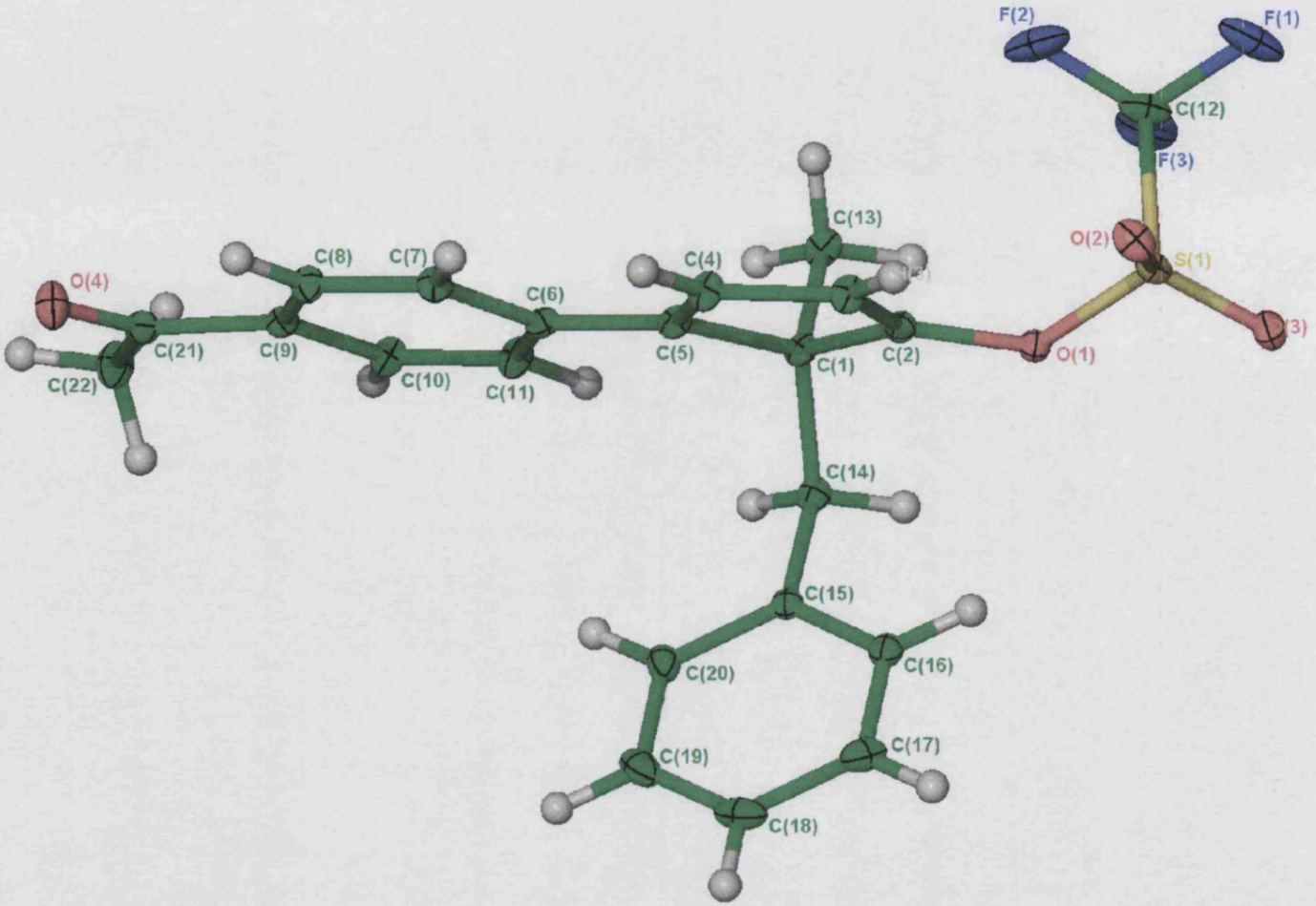


Table 1. Crystal data and structure refinement for 1.

Identification code	k01mcw5
Empirical formula	C22 H19 F3 O4 S
Formula weight	436.43
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 7.1490(2)Å α = 99.604(2)°
	b = 7.7770(2)Å β = 95.277(2)°
	c = 9.4750(2)Å γ = 103.5760(10)°
Volume	500.14(2) $Å^3$
Z	1
Density (calculated)	1.449 Mg/m^3
Absorption coefficient	0.216 mm^{-1}
F(000)	226
Crystal size	0.40 x 0.30 x 0.30 mm
Theta range for data collection	3.84 to 30.04°
Index ranges	-10<=h<=10; -10<=k<=10; -13<=l<=13
Reflections collected	9618
Independent reflections	5253 [R(int) = 0.0306]
Reflections observed (>2σ)	5109
Data Completeness	0.988
Max. and min. transmission	0.9380 and 0.9185
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5253 / 3 / 274
Goodness-of-fit on F^2	1.013
Final R indices [I>2σ(I)]	R_1 = 0.0300 wR_2 = 0.0775
R indices (all data)	R_1 = 0.0312 wR_2 = 0.0786
Absolute structure parameter	-0.02(4)
Largest diff. peak and hole	0.259 and -0.219 $eÅ^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for 1.U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
S(1)	3646(1)	15355(1)	10962(1)	25(1)
F(1)	5542(2)	18460(2)	12392(2)	63(1)
F(2)	6391(2)	17811(2)	10273(2)	65(1)
F(3)	7325(2)	16610(2)	11990(1)	52(1)
O(1)	4322(1)	13846(1)	9979(1)	24(1)
O(2)	2268(2)	16020(2)	10198(1)	34(1)
O(3)	3335(2)	14736(2)	12264(1)	34(1)
O(4)	9914(2)	11354(2)	708(1)	37(1)
C(1)	6069(2)	12958(2)	7954(1)	22(1)
C(2)	4530(2)	13822(2)	8502(1)	23(1)
C(3)	3546(2)	14411(2)	7500(2)	27(1)
C(4)	4381(2)	14000(2)	6168(2)	27(1)
C(5)	5832(2)	13176(2)	6382(2)	23(1)
C(6)	7035(2)	12652(2)	5291(2)	23(1)
C(7)	6771(2)	13069(2)	3913(2)	26(1)
C(8)	7858(2)	12592(2)	2851(2)	27(1)
C(9)	9285(2)	11680(2)	3123(2)	24(1)
C(10)	9605(2)	11298(2)	4494(2)	28(1)
C(11)	8492(2)	11769(2)	5560(2)	29(1)
C(12)	5883(2)	17179(2)	11421(2)	38(1)
C(13)	8079(2)	14051(2)	8767(2)	29(1)
C(14)	5652(2)	10969(2)	8177(2)	25(1)
C(15)	3769(2)	9735(2)	7364(1)	23(1)
C(16)	2032(2)	9629(2)	7945(2)	28(1)
C(17)	313(2)	8443(2)	7228(2)	37(1)
C(18)	292(3)	7357(2)	5911(2)	42(1)
C(19)	2000(3)	7455(2)	5311(2)	40(1)
C(20)	3729(2)	8634(2)	6025(2)	32(1)
C(21)	10346(2)	11102(2)	1916(2)	27(1)
C(22)	11910(2)	10156(2)	2212(2)	37(1)

Table 3. Bond lengths [Å] and angles [°] for 1.

S(1)-O(2)	1.4124(11)	S(1)-O(3)	1.4146(11)
S(1)-O(1)	1.5695(9)	S(1)-C(12)	1.8331(16)
F(1)-C(12)	1.322(2)	F(2)-C(12)	1.312(2)
F(3)-C(12)	1.3192(19)	O(1)-C(2)	1.4187(16)
O(4)-C(21)	1.2173(19)	C(1)-C(2)	1.5055(18)
C(1)-C(5)	1.5261(18)	C(1)-C(13)	1.5440(19)
C(1)-C(14)	1.5587(18)	C(2)-C(3)	1.3345(19)
C(3)-C(4)	1.4641(19)	C(4)-C(5)	1.3581(18)
C(5)-C(6)	1.4698(18)	C(6)-C(11)	1.4029(18)
C(6)-C(7)	1.4039(19)	C(7)-C(8)	1.3813(19)
C(8)-C(9)	1.4004(19)	C(9)-C(10)	1.3909(19)
C(9)-C(21)	1.4945(19)	C(10)-C(11)	1.3950(19)
C(14)-C(15)	1.5106(19)	C(15)-C(16)	1.3944(18)
C(15)-C(20)	1.4012(18)	C(16)-C(17)	1.388(2)
C(17)-C(18)	1.381(3)	C(18)-C(19)	1.386(3)
C(19)-C(20)	1.391(3)	C(21)-C(22)	1.506(2)
O(2)-S(1)-O(3)	122.53(7)	O(2)-S(1)-O(1)	112.60(6)
O(3)-S(1)-O(1)	105.80(6)	O(2)-S(1)-C(12)	106.68(7)
O(3)-S(1)-C(12)	105.16(8)	O(1)-S(1)-C(12)	101.93(7)
C(2)-O(1)-S(1)	123.80(8)	C(2)-C(1)-C(5)	99.82(10)
C(2)-C(1)-C(13)	109.28(11)	C(5)-C(1)-C(13)	111.71(10)
C(2)-C(1)-C(14)	110.14(10)	C(5)-C(1)-C(14)	114.96(11)
C(13)-C(1)-C(14)	110.39(11)	C(3)-C(2)-O(1)	130.24(12)
C(3)-C(2)-C(1)	114.20(12)	O(1)-C(2)-C(1)	115.55(11)
C(2)-C(3)-C(4)	105.75(12)	C(5)-C(4)-C(3)	111.28(12)
C(4)-C(5)-C(6)	125.47(13)	C(4)-C(5)-C(1)	108.94(12)
C(6)-C(5)-C(1)	125.54(11)	C(11)-C(6)-C(7)	117.02(12)
C(11)-C(6)-C(5)	123.21(12)	C(7)-C(6)-C(5)	119.76(12)
C(8)-C(7)-C(6)	121.76(12)	C(7)-C(8)-C(9)	120.70(12)
C(10)-C(9)-C(8)	118.42(12)	C(10)-C(9)-C(21)	122.84(12)
C(8)-C(9)-C(21)	118.70(12)	C(9)-C(10)-C(11)	120.67(12)
C(10)-C(11)-C(6)	121.39(13)	F(2)-C(12)-F(3)	108.52(15)
F(2)-C(12)-F(1)	110.46(15)	F(3)-C(12)-F(1)	108.70(15)
F(2)-C(12)-S(1)	111.13(12)	F(3)-C(12)-S(1)	110.86(11)
F(1)-C(12)-S(1)	107.16(12)	C(15)-C(14)-C(1)	115.36(11)
C(16)-C(15)-C(20)	118.23(13)	C(16)-C(15)-C(14)	120.80(12)
C(20)-C(15)-C(14)	120.95(12)	C(17)-C(16)-C(15)	120.94(14)
C(18)-C(17)-C(16)	120.35(16)	C(17)-C(18)-C(19)	119.56(16)
C(18)-C(19)-C(20)	120.43(15)	C(19)-C(20)-C(15)	120.49(15)
O(4)-C(21)-C(9)	120.30(13)	O(4)-C(21)-C(22)	120.82(13)
C(9)-C(21)-C(22)	118.86(12)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for 1. The anisotropic displacement
factor exponent takes the form: $-2\ gpi^2\ [\ h^2\ a^{*2}\ U11 + ... + 2\ h\ k\ a^*\ b^*\ U$

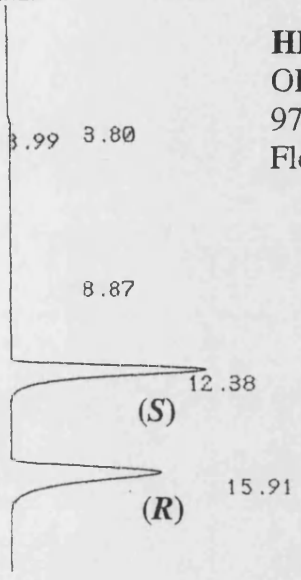
Atom	U11	U22	U33	U23	U13	U12
S(1)	23(1)	21(1)	28(1)	1(1)	0(1)	6(1)
F(1)	44(1)	33(1)	93(1)	-24(1)	-8(1)	6(1)
F(2)	56(1)	45(1)	88(1)	31(1)	7(1)	-12(1)
F(3)	28(1)	44(1)	75(1)	-1(1)	-13(1)	8(1)
O(1)	28(1)	22(1)	24(1)	5(1)	5(1)	8(1)
O(2)	30(1)	36(1)	36(1)	1(1)	-3(1)	16(1)
O(3)	41(1)	33(1)	28(1)	2(1)	9(1)	12(1)
O(4)	44(1)	48(1)	26(1)	8(1)	9(1)	21(1)
C(1)	21(1)	25(1)	24(1)	10(1)	4(1)	8(1)
C(2)	23(1)	22(1)	23(1)	6(1)	5(1)	7(1)
C(3)	26(1)	31(1)	30(1)	10(1)	5(1)	14(1)
C(4)	27(1)	34(1)	27(1)	13(1)	5(1)	14(1)
C(5)	21(1)	26(1)	25(1)	9(1)	3(1)	7(1)
C(6)	21(1)	22(1)	26(1)	9(1)	4(1)	6(1)
C(7)	28(1)	26(1)	27(1)	8(1)	3(1)	11(1)
C(8)	31(1)	28(1)	23(1)	8(1)	4(1)	11(1)
C(9)	23(1)	24(1)	26(1)	6(1)	5(1)	4(1)
C(10)	24(1)	34(1)	30(1)	12(1)	6(1)	13(1)
C(11)	27(1)	38(1)	28(1)	15(1)	7(1)	15(1)
C(12)	29(1)	23(1)	56(1)	1(1)	-4(1)	2(1)
C(13)	23(1)	36(1)	29(1)	11(1)	1(1)	7(1)
C(14)	27(1)	27(1)	26(1)	11(1)	6(1)	12(1)
C(15)	31(1)	19(1)	24(1)	8(1)	7(1)	10(1)
C(16)	33(1)	23(1)	30(1)	8(1)	9(1)	10(1)
C(17)	33(1)	28(1)	51(1)	15(1)	9(1)	6(1)
C(18)	47(1)	23(1)	49(1)	11(1)	-9(1)	1(1)
C(19)	65(1)	24(1)	31(1)	2(1)	1(1)	12(1)
C(20)	47(1)	26(1)	27(1)	6(1)	12(1)	16(1)
C(21)	26(1)	25(1)	30(1)	4(1)	5(1)	6(1)
C(22)	37(1)	45(1)	36(1)	11(1)	12(1)	21(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 1.

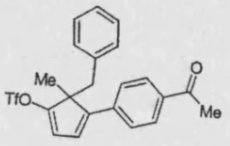
Atom	x	y	z	U(eq)
H(3)	2517	14981	7624	33
H(4)	3961	14273	5270	33
H(7)	5820	13697	3705	31
H(8)	7635	12884	1927	32
H(10)	10591	10711	4708	33
H(11)	8727	11485	6486	34
H(13A)	8322	15297	8616	43
H(13B)	9087	13507	8399	43
H(13C)	8103	14045	9802	43
H(14A)	6735	10464	7878	30
H(14B)	5640	10971	9221	30
H(16)	2025	10379	8844	33
H(17)	-854	8379	7644	44
H(18)	-887	6548	5421	50
H(19)	1990	6711	4405	49
H(20)	4891	8694	5602	38
H(22A)	12579	9997	1361	55
H(22B)	11323	8973	2428	55
H(22C)	12845	10881	3041	55

Appendix-4

CHANNEL A INJECT 10-09-22 05:58:31 STORED TO BIN # 2



HPLC trace of racemic monotriflate 247
OD Chiralcel column
97-3 Hexane-*I*prOH
Flow rate 0.8 mL/min



DATA SAVED TO BIN # 2

10-09-22 05:58:31 CH= "A" PS= 1.

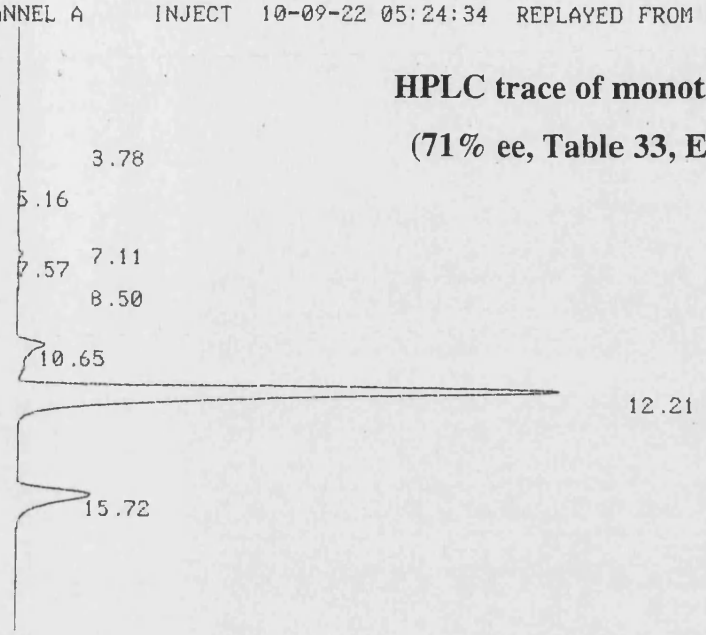
FILE 1. METHOD 0. RUN 2 INDEX 2 BIN 2

PEAK#	AREA%	RT	AREA	BC
1	0.055	3.8	5532	02
2	0.156	3.99	15693	03
3	0.463	8.87	46539	01
4	49.183	12.38	4943303	01
5	50.143	15.91	5039779	01
TOTAL	100.		10050846	

CHANNEL A INJECT 10-09-22 05:24:34 REPLAYED FROM BIN # 1

HPLC trace of monotriflate 247

(71% ee, Table 33, Entry 4)

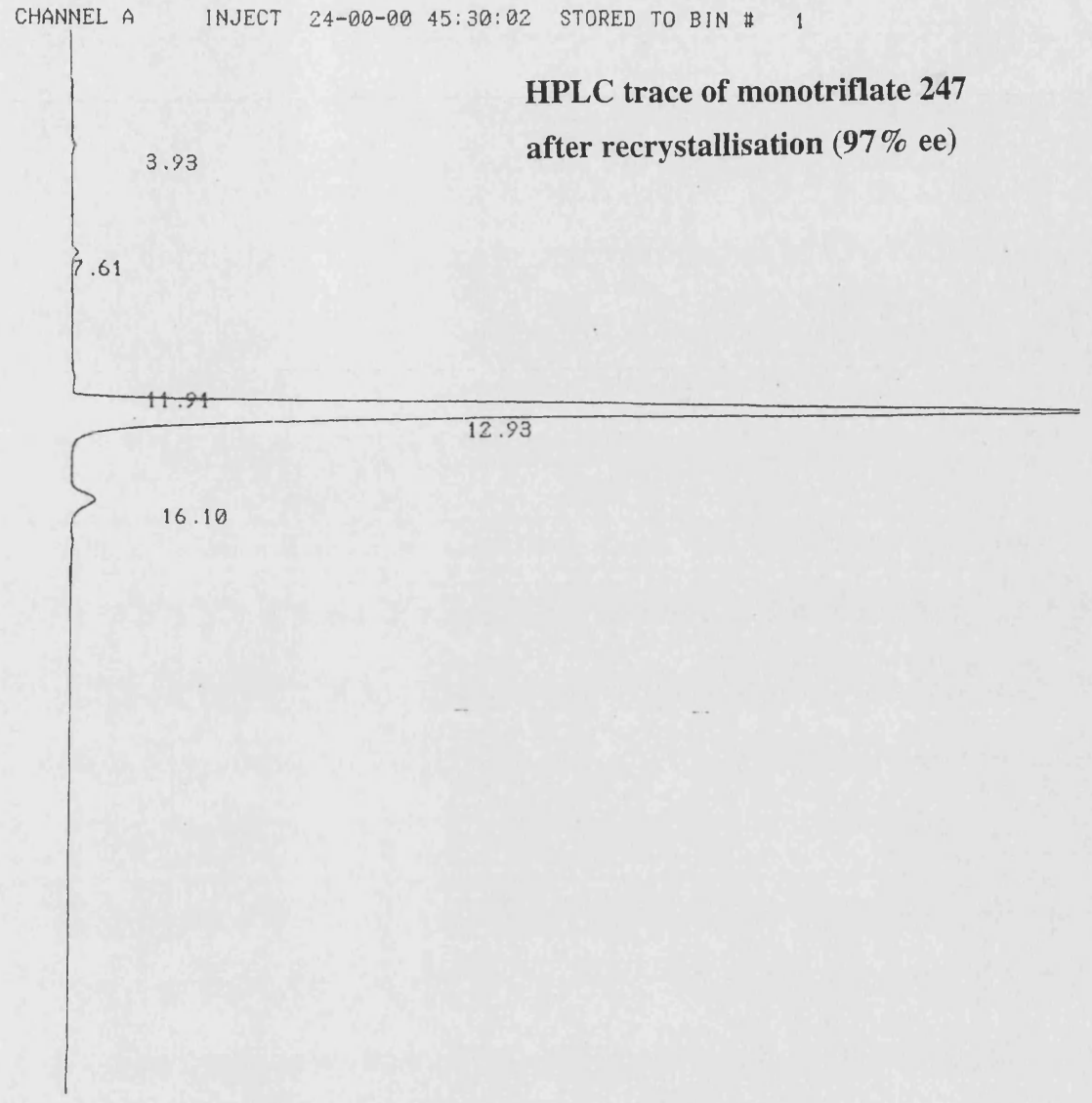


10-09-22 05:24:34 CH= "A" PS= 1.

FILE 1. METHOD 0. RUN 7 INDEX 7 BIN 1

PEAK#	AREA%	RT	AREA	BC
1	0.099	3.78	16510	01
2	0.056	5.16	9315	01
3	0.139	7.11	23092	02
4	0.316	7.57	52635	03
5	0.126	8.5	20987	01
6	3.362	10.65	559692	01
7	81.884	12.21	13630241	01
8	14.017	15.72	2333319	01
TOTAL	100.		16645791	

HPLC trace of monotriflate 247 after recrystallisation (97% ee)



DATA SAVED TO BIN # 1

24-00-00 45:30:02 CH= "A" PS= 1.

FILE 1. METHOD 0. RUN 1 INDEX 1 BIN 1

PEAK#	AREA%	RT	AREA	BC
1	0.099	3.93	15767	01
2	0.251	7.61	40127	01
3	0.206	11.91	32945	02
4	97.094	12.93	15501476	03
5	2.349	16.1	375092	01
TOTAL	100.		15965407	